Table 6 - Demographics (All Subjects) – Study 005

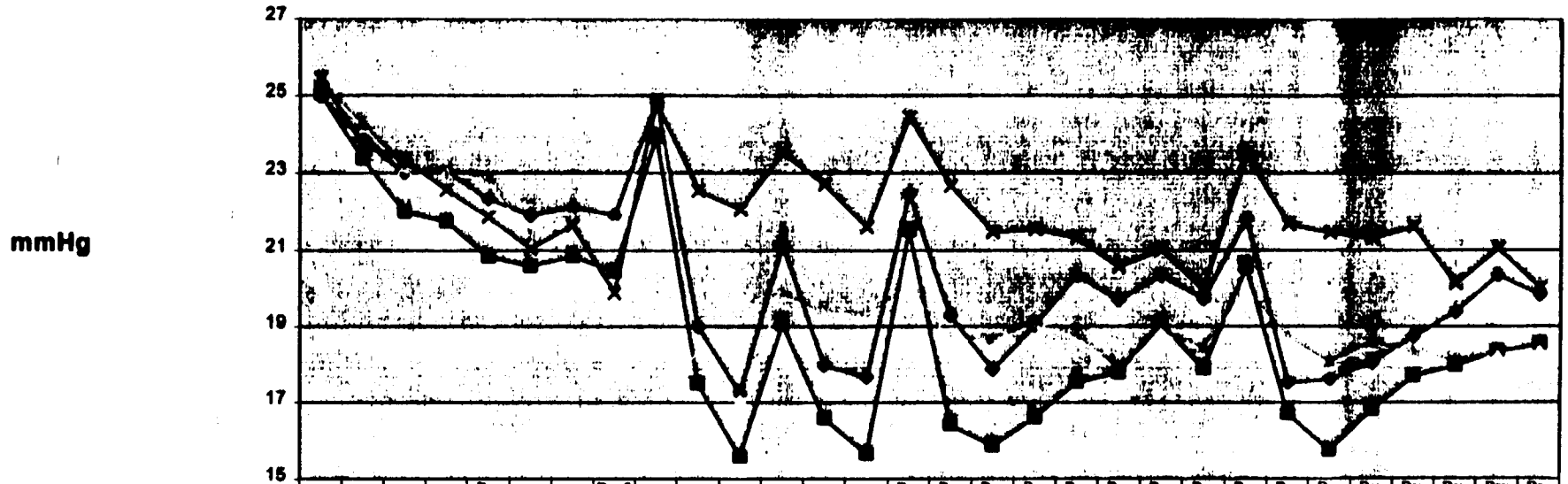
		0.1% (N=30)	0.2% (N=30)	(N=31)	(N=31)	
Age	Mean	58.8	61.1	59.9	63.8	0.445
	Std	13.9	12.4	13.8	12.7	
	Min	22.4	39.4	30.6	33.3	
	Max	84.0	81.1	81.9	89.6	
Age group						
< 45	N	4 (13.3%)	4 (13.3%)	6 (19.4%)	3 (9.7%)	
45 - 65	N	12 (40.0%)	13 (43.3%)	12 (38.7%)	12 (38.7%)	
> 65	N	14 (46.7%)	13 (43.3%)	13 (41.9%)	16 (51.6%)	
Sex						
Male	N	16 (53.3%)	14 (46.7%)	14 (45.2%)	15 (48.4%)	0.936
Female	N	14 (46.7%)	16 (53.3%)	17 (54.8%)	16 (51.6%)	
Race						
Caucasian	N	25 (83.3%)	23 (76.7%)	23 (74.2%)	23 (74.2%)	0.725
Black	N	2 (6.7%)	4 (13.3%)	4 (12.9%)	5 (16.1%)	
Hispanic	N	3 (10%)	3 (10%)	4 (12.9%)	3 (9.7%)	
Iris Color						
Blue	N	4 (13.3%)	8 (26.7%)	9 (29%)	6 (19.4%)	0.498
Brown	N	18 (60%)	17 (56.7%)	15 (48.4%)	13 (41.9%)	
Green	N	2 (6.7%)	0	1 (3.2%)	3 (9.7%)	
Hazel	N	6 (20%)	5 (16.7%)	6 (19.4%)	7 (22.6%)	
Other	N	0	0	0	2 (6.5%)	
Light		12 (40%)	13 (43.3%)	16 (51.6%)	18 (58.1%)	
Dark		18 (60%)	17 (56.7%)	15 (48.4%)	13 (41.9%)	

Reviewers Comments:

There were no significant differences in demographics between the treatment groups.

Reviewers Comments: *A per protocol analysis of the data was performed. The population for the intent-to-treat population is the same since no patients were excluded from the study.*

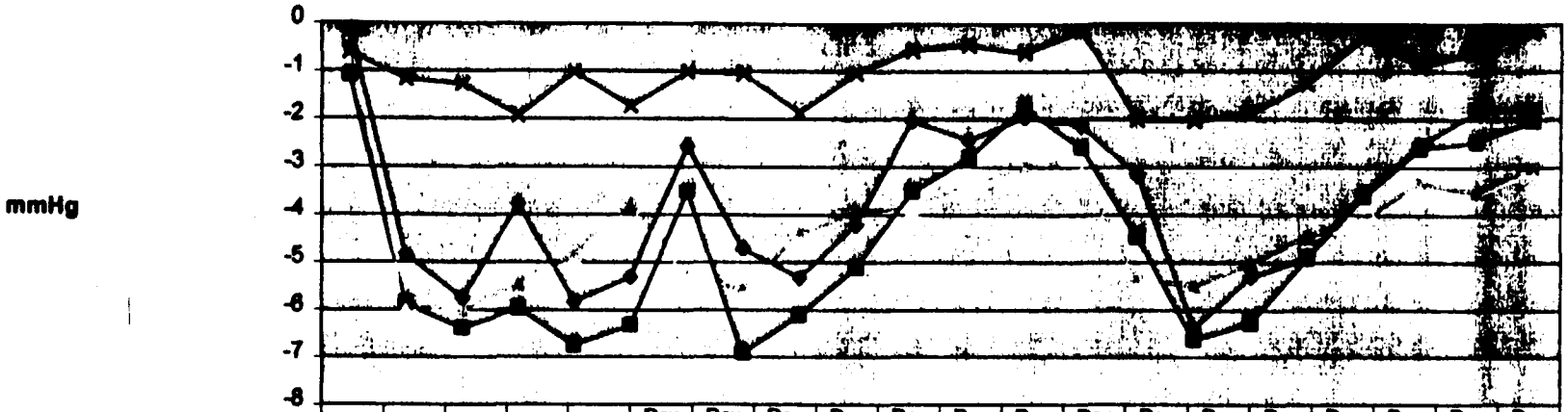
Mean Diurnal IOP - Study 005



	Day 0 (hr 0)	Day 0 (hr 1)	Day 0 (hr 2)	Day 0 (hr 3)	Day 0(hr 5)	Day 0 (hr 7)	Day 0 (hr 9)	Day 0 (hr 12)	Day 1 (hr 0)	Day 1 (hr 1)	Day 1 (hr 2)	Day 7 (hr 0)	Day 7 (hr 1)	Day 7 (hr 2)	Day 21 (hr 0)	Day 21 (hr 1)	Day 21 (hr 2)	Day 21 (hr 3)	Day 21 (hr 5)	Day 21 (hr 7)	Day 21 (hr 9)	Day 21 (hr 12)	Day 28 (hr 0)	Day 28 (hr 1)	Day 28 (hr 2)	Day 28 (hr 3)	Day 28 (hr 5)	Day 28 (hr 7)	Day 28 (hr 9)	Day 28 (hr 12)
Brimonidine-Purite 0.1%	24.98	23.85	23	23.05	22.32	21.9	22.12	21.9	24.83	19	17.25	21.14	17.98	17.67	22.47	19.28	17.86	19.02	20.34	19.69	20.34	19.73	21.8	17.52	17.61	18.07	18.73	19.39	20.34	19.82
Brimonidine-Purite 0.2%	25.03	23.35	21.98	21.73	20.82	20.58	20.83	20.43	23.93	17.47	15.58	19.05	16.58	15.65	21.5	16.42	15.85	16.6	17.53	17.77	19.07	17.88	20.55	16.7	15.74	16.8	17.69	17.97	18.35	18.53
Timoptic 0.5%	25.37	24.26	23.11	23.06	22.82	21.35	21.89	21.66	24.77	18.29	17.08	19.87	19.37	19.29	20.03	18.65	18.68	19.08	18.77	17.89	18.84	18.42	19.98	18.73	18.06	18.56	18.34	18.1	18.31	18.42
Vehicle	25.45	23.71	23.32	22.56	21.84	21.02	21.63	19.87	24.82	22.53	22.03	23.5	22.69	21.58	24.44	22.65	21.45	21.52	21.29	20.55	21	19.94	23.42	21.66	21.44	21.29	21.6	20.11	21.02	20

Reviewers Comments: *Brimonidine Purite 0.2% has a greater IOP lowering ability than Brimonidine Purite 0.1 % at all time points. Both the 0.1% and the 0.2 % lower IOP more than vehicle at the majority of timepoints.*

Mean IOP Change from Baseline - Study 005



	Day 1 (hr 0)	Day 1 (hr 1)	Day 1 (hr 2)	Day 7 (hr 0)	Day 7 (hr 1)	Day 21 (hr 0)	Day 21 (hr 1)	Day 21 (hr 2)	Day 21 (hr 3)	Day 21 (hr 5)	Day 21 (hr 7)	Day 21 (hr 9)	Day 21 (hr 12)	Day 28 (Hr 0)	Day 28 (Hr 1)	Day 28 (Hr 3)	Day 28 (Hr 5)	Day 28 (Hr 7)	Day 28 (Hr 9)	Day 28 (Hr 12)
Brimonidine-Purite 0.1%	-0.15	-4.85	-5.75	-3.78	-5.83	-2.57	-4.72	-5.33	-4.22	-2.04	-2.43	-1.97	-2.12	-3.16	-6.38	-4.93	-3.54	-2.54	-1.84	-1.8
Brimonidine-Purite 0.2%	-1.1	-5.88	-6.4	-5.96	-6.77	-3.53	-6.93	-6.13	-5.13	-3.53	-2.82	-1.77	-2.6	-4.48	-6.65	-4.93	-3.63	-2.62	-2.48	-2.05
Timoptic 0.5%	-0.6	-5.97	-6.03	-5.5	-4.89	-5.34	-5.61	-4.44	-3.96	-3.87	-3.45	-3.05	-3.11	-5.39	-5.53	-4.5	-4.14	-3.35	-3.58	-3.03
[redacted] Vehicle	-0.63	-1.18	-1.29	-1.95	-1.02	-1.02	-1.06	-1.87	-1.05	-0.58	-0.47	-0.63	-0.16	-2.03	-2.05	-1.27	-0.31	-0.9	-0.61	-0.19

Reviewers Comments:

Brimonidine 0.1% and 0.2% fail to lower IOP by 20 % at trough. There are clinically significant diurnal fluctuations in the IOP lowering effect of both the 0.1% and 0.2% formulations. IOP reduction in the timolol group was less than the amount expected based on previous studies (i.e., 4.5 - 7 mmHg)

Safety

Table 7 - Number(%) of Patients with Adverse Events Reported by ≥ 2% of Patients in Any 1 Treatment Group – Study 005

Reaction Term	Brimonidine-Purite 0.1% (N=30)		Brimonidine-Purite 0.2% (N=30)		Timoptic 0.5% (N=31)		Vehicle (N=31)	
Ocular								
Allergic Reaction	0		0		1	3.2%	0	
Asthenia	0		0		2	6.5%	0	
Asthenopia	0		1	3.3%	0		0	
Burning Eye	2	6.7%	0		1	3.2%	0	
Conjunctival Folliculosis	0		1	3.3%	0		0	
Conjunctivitis Hemorrhagic	0		0		0		1	3.2%
Dry Eye	0		1	3.3%	0		0	
Foreign Body Sensation	2	6.7%	0		0		1	3.2%
Hyperemia Conjunctival	0		3	10%	0		1	3.2%
Keratitis Superficial Punctate	0		1	3.3%	0		0	
Photopsia	0		0		1	3.2%	0	
Pruritus Eye	0		1	3.3%	1	3.2%	0	
Stinging Eye	1	3.3%	0		1	3.2%	0	
Visual Disturbance	2	6.7%	0		0		1	3.2%
Non-Ocular								
Anxiety	1	3.3%	0		1	3.2%	0	
Dizziness	1	3.3%	1	3.3%	0		1	3.2%
Dryness Oral	1	3.3%	1	3.3%	0		1	3.2%
Flu Syndrome	0		0		1	3.2%	0	
Headache	2	6.7%	4	13.3%	1	3.2%	1	3.2%
Hemmorhage Vaginal	0		0		1	3.2%	0	
Infection	1	3.3%	1	3.3%	1	3.2%	0	
Infection Sinus	0		0		0		1	3.2%
Injury Accident	0		0		0		1	3.2%
Migraine	0		1	3.3%	0		0	
Nausea	1	3.3%	0		0		0	
Nausea Vomiting	1	3.3%	0		0		0	
Nervousness	0		1	3.3%	0		0	
Neuropathy	1	3.3%	0		0		0	
Pain Leg	1	3.3%	0		0		0	
Palpitations	0		0		1	3.2%	0	
Pharyngitis	0		0		1	3.2%	0	
Prostate Disease	0		0		1	3.2%	0	
Rhinitis	0		0		1	3.2%	0	
Sinusitis	0		0		0		1	3.2%
Somnolence	0		2	6.7%	1	3.2%	1	3.2%

Visual Acuity

Table 8 - Visual Acuity Change from Baseline – Study 005

Visual Acuity Change (lines)	Brimonidine Purite 0.1% (N=30)	Brimonidine-Purite 0.2% (N=30)	Timoptic 0.5% (N=31)	Vehicle
≥-2	1 (3.3%)	1 (3.3%)	1 (3.2%)	0
-2 to +2	29 (96.7%)	29 (96.7%)	30 (96.8%)	31 (100%)
≥ 2	0	0	0	0

Reviewers Comments:
There were no clinically significant differences in visual acuity between treatment groups. There were no clinically significant changes from baseline in visual acuity for any of the treatment groups.

Cup-Disc Ratio

Reviewers Comments:
There were no statistically or clinically significant mean changes from baseline in any treatment group or any significant between-group differences.

Heart Rate/Blood Pressure

Reviewer's Comments:
There were clinically significant mean changes from baseline in any of the treatment groups.

Reviewers Summary of Safety and Efficacy

Brimonidine Purite 0.2% has greater IOP lowering ability than Brimonidine Purite 0.1% at all timepoints throughout this study.

Brimonidine Purite 0.1% and 0.2% fail to lower IOP by 20% at trough.

The number of patients with both ocular and non-ocular adverse events were similar for Brimonidine Purite 0.1% and 0.2%. The most frequently reported events were headache and conjunctival hyperemia.

8.2 Study #2 Protocol 190342-007

Title: A Multicenter, Double-Masked, Randomized, Parallel, 3-Month Study (with an Extension to 1 year) of the Safety, Efficacy, and Acceptability of 0.15% and 0.2% Brimonidine-Purite™ Compared with 0.2% Brimonidine Administered 3-Times-Daily in Subjects with Glaucoma or Ocular Hypertension

Objective: To evaluate the safety, efficacy , and acceptability of Brimonidine-Purite™ 0.15% and 0.2% compared with Brimonidine 0.2% (Alphagan®) administered 3-times daily (TID) for 3 months (with treatment extended to 1 year) in patients with glaucoma or ocular hypertension (OHT).

Study Design: A Multicenter, Double-Masked, Active-Controlled, Randomized, Parallel Group Study.

Test Drug Schedule: Patients were instructed to instill 1 drop of study medication into each eye TID daily for 3 months.

Table 9 - Clinical Sites – Study 007

Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	Number of Subjects Enrolled	Subject ID Series
Richard S. Bennion, M.D. (2973) Wenatchee Valley Clinic Research Dept. 820 North Chelan Wenatchee, WA 98801		33	N01-N33
E. Randy Craven, M.D. (2027) Glaucoma Consultants of Colorado 8381 South Park Lane Littleton, CO 80120		35	F01-F35
Richard Evans, M.D. (2975) Keystone Research 9150 Huebner, Suite 280 San Antonio, TX 78229		35	V01-V35

Principal Investigator (Number of Subjects)	Other Important Participants (Degree)	Number of Subjects Enrolled	Subject ID Series
Maher Fanous, M.D./ Gary N. Foulks, M.D. (2976) University of Pittsburgh The Eye and Ear Institute 203 Lothrop Street rm. 827 Pittsburgh, PA 15213	Francis S. Mah, M.D. (subinvestigator)	2	X01-X02
William C. Flynn, M.D. (3047) 999 E. Basse, Ste. 116 San Antonio, TX 78209	Stephen Waller, M.D. (subinvestigator) Monte Dirks, M.D. (subinvestigator) Steven Grimes, M.D. (subinvestigator)	14	E01-E14
Daniel Foreman, M.D. (2977) Clinical Research, Inc. 6620 Coyle Avenue, Suite 300 Carmichael, CA 95608	Dena Davidson, O.D. (subinvestigator)	17	D01-D17
Stephen Gee, M.D. (2978) 1210 Ward Ave. Honolulu, Oahu, HI 96814		3	M01-M03
Charles S. Ostrov, M.D. (1796) Medical Vision Center Apache Medical Building 4001 Stinson Blvd., N.E., Suite 224 Minneapolis, MN 55421	Bonnie Bongard, M.D. (subinvestigator)	26	T01-T26
Michael J. Price, M.D., FRCSC (1183) 578 Main St. Malden, MA 02148	Mehmoosh Ashabi, O.D. (subinvestigator)	40	J01-J40
Edward R. Rashid, M.D. (1819) Keystone Research 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	Robert A. Rice, M.D. (subinvestigator)	15	Y01-Y15
Kenneth Sall, M.D. (2707) Sall Eye Surgery Center 9604 E. Artesia Blvd., Suite 203 Bellflower, CA 90706	Krzysztof Gwizdak, O.D. (subinvestigator) Delaware F. Harris II, M.D. (subinvestigator)	48	S01-S48
John Samples, M.D. (0622) Casey Eye Institute Oregon Health Sciences 3375 SW Terwilliger Blvd. Portland, OR 97201-4197		2	C01-C02
Gail F. Schwartz, M.D., P.A. (2944) GBMC Physicians Pavilion East 6565 N. Charles Street, Suite 316 Baltimore, MD 21204	Babak Eliassi-Rad, M.D. (subinvestigator) Lisa Abrams, M.D. (subinvestigator)	32	K01-K32

Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	Number of Subjects Enrolled	Subject ID Series
John D. Sheppard, M.D. (2091) VA Eye Consultants 403 Medical Tower Norfolk, VA 23507-1901	Bruce I. Bodner, M.D. (subinvestigator) April S. Rusch, B.S., COMT, CCRC (subinvestigator) Peter V. Mitrev, M.D. (subinvestigator)	28	L01-L28
Dong H. Shin, M.D., Ph.D. (0136) Detroit Medical Center University Eye Associates, P.C. Kresge Eye Institute 4717 St. Antoine Detroit, MI 48201-1423	Padmaja Nootheti, M.D. (subinvestigator) Bret A. Hughs, M.D. (subinvestigator) Mark S. Juzych, M.D. (subinvestigator)	4	W01-W04
Dara Stevenson, M.D. (2366) Stevenson Eye Center 3535 Bienville St., Ste. 325 East New Orleans, LA 70119		48	Z01-Z48
William C. Stewart, M.D. (1783) Atlanta Research Company 2814 Spring Road, Suite 230 Atlanta, GA 30339	Douglas Day, M.D. (subinvestigator)	28	U01-U28
Lloyd Suter, M.D. (2985) Twin Tiers Eye Care Associates 40 Mitchell Ave. Binghamton, NY 13903	Francis Gilroy, M.D. (subinvestigator)	15	H01-H15
Thomas R. Walters, M.D. (1634) 1700 South Mopac Austin, TX 78746	James Montgomery, M.D. (subinvestigator)	46	B01-B46
Robert D. Williams, M.D. (2710) Taustine Eye Center Medical Arts Building 1169 Eastern Parkway, Suite 3334 Louisville, KY 40217	Lloyd R. Taustine, M.D. (subinvestigator) Brian K. Kritchman, M.D. (subinvestigator)	39	G01-G39
Lisa Wohl, M.D., S.C. (2986) Wohl Eye Center Willowlake Centre, Suite 200 303 E. Army Trail Rd. Bloomingdale, IL 60108		18	R01-R18
Brandon Wool, M.D. (2835) 315 Metairie Road, Ste. 302 Metairie, LA 70005		18	P01-P18

Selection of Study Population

Inclusion Criteria

The following were requirements for entry into the study:

- Patients were at least 18 years old and of legal age of consent
- Patients had glaucoma (including primary, pseudoexfoliative, pigment dispersion, chronic angle-closure with a patent peripheral iridectomy/iridotomy for at least 3 months) or ocular hypertension in each eye
- Patients were likely to be controlled on monotherapy
- Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity of 20/100 (Snellen equivalent) or better in each eye
- Written informed consent had been obtained
- Patients had the ability to follow study instructions and were likely to complete all required visits
- Baseline (day 0), hour 0: IOP of $\geq$ 22 mm Hg and $\leq$ 34 mm Hg in each eye and asymmetry of IOP not greater than 5 mm Hg
- Baseline (day 0): for women of childbearing potential, a negative pregnancy test result was required. A woman was considered of childbearing potential unless she was postmenopausal, without a uterus and/or both ovaries removed, or had had a bilateral tubal ligation.
- Baseline (day 0): 2 reliable visual fields should have been on file before dosing. Prestudy visual fields could have been performed up to 6 months prior to the prestudy visit. Day 0 visual field should have been performed between the prestudy and day 0 visits.

Exclusion Criteria

The following were criteria for exclusion from participating in this study:

- Uncontrolled systemic disease
- Women who were pregnant, nursing, or planning a pregnancy or who were of childbearing potential and not using a reliable form of contraception
- Abnormally low or high blood pressure or heart rate for age

- Known allergy or sensitivity to any of the study medication ingredients
- Contraindications to brimonidine therapy, such as concurrent use of monoamine oxidase (MAO) inhibitor therapy
- Anticipated alteration of existing chronic therapy with agents which could have had a substantial effect on IOP, including but not limited to, systemic adrenergic agents including beta-adrenergic blocking agents (eg, propanolol, metoprolol, nadolol, timolol, atenolol)
- Anticipated treatment with adrenergic-augmenting psychotropic drugs (eg, desipramine, amitriptyline)
- Any other active ocular disease (eg, uveitis, ocular infections, or severe dry eye). However, patients with chronic mild blepharitis, cataract, age-related macular degeneration, or background diabetic retinopathy could have been enrolled at the discretion of the investigator
- Corneal abnormalities that would preclude accurate readings with an applanation tonometer
- Anticipated wearing of contact lenses during the study (use of soft lenses should have been discontinued at least 2 days prior to day 0, and use of RGP or hard contact lenses should have been discontinued at least 1 month prior to day 0)
- Any glaucoma other than those listed in the inclusion criteria
- Required chronic use of other ocular medications during the study (intermittent use of artificial tear product was allowed)
- Refractive, laser, filtering or any other ocular surgery within the past 3 months
- Patients who had corneal grafts or refractive surgery (for sites performing endothelial cell counts)
- Visual field loss which in the opinion of the investigator was functionally significant, or evidence of progressive visual field loss within the previous year
- Contraindications to pupil dilation
- Participation in a drug or device research study 30 days prior to entry into this study or concurrent participation in any other drug or device research study
- Patient had a condition or was in a situation that, in the investigator's opinion, might have put the patient at significant risk, might have confounded study results, or might have interfered significantly with the patient's participation in the study

- Baseline (day 0): Patients who had not been appropriately washed out of their antiglaucoma medications

Study Medications

Brimonidine-Purite 0.15% ophthalmic solution (Allergan formulation number 9174X, lot numbers 11371, 11384, 11394, and 11522) contains brimonidine tartrate 0.15% with [redacted] (Purite) 0.005%, and carboxymethylcellulose sodium [redacted] purified water, boric acid, sodium borate, [redacted] hydrochloric acid and/or sodium hydroxide to adjust pH.

Brimonidine-Purite 0.2% ophthalmic solution (Allergan formulation number 9115X, lot numbers 11286, 11393, 11432, and 11523) contains brimonidine tartrate 0.2% with [redacted]

Brimonidine tartrate 0.2% ophthalmic solution (ALPHAGAN) (Allergan formulation number 7831X, lot number 11390) [redacted]

Study Masking

Study medications were dispensed in identical dropper bottles containing 15 mL of solution. There was no unmasking during this study.

Efficacy Variables

IOP was the primary efficacy variable, and was measured in mm Hg using a [redacted] affixed to a slit lamp, with the patient in a sitting position. In this study patients were treated bilaterally. During testing, the right eye was measured first and the left eye measured second; during data analysis the average IOP from both eyes was used. At return visits, IOP was measured at trough (hour 0). Thus patients had to have taken their last medication in the evening (between 09:30 PM and 10:30 PM) and postponed their morning instillation of eyedrops until after their examination, when the investigator administered the drops. In addition to trough evaluation of IOP, diurnal measurements were also made to ensure continued IOP reduction throughout the day. After administration of medication, IOP diurnal measurements were made at hours 2, 7, and 9 at the baseline, week 6, months 3, 6, and 12 follow-up visits. In addition, IOP was measured at hour 2 at the week 2 and month 9 follow-up visits.

Safety Variables

Visual Acuity
Best-corrected visual acuity was measured for each eye using a standard ETDRS chart and procedures.

Biomicroscopy
Biomicroscopy was performed without pupil dilation using slit-lamp examination with fluorescein. The examinations included evaluation of the condition of the lid/lashes (erythema/hyperemia, edema), conjunctiva (erythema/hyperemia, edema, follicles, blanching), cornea (edema, staining/erosion, endothelial pigment, endothelial dystrophy), anterior chamber (cells, flare, anterior synechiae, posterior synechiae), and lens pathology (cataract). Observations were recorded using a 5-point scale (0 = none, 0.5 = trace 1 = mild, 2 = moderate, and 3 = severe). Iris pathology and vitreous pathology were evaluated for the presence or absence of clinically significant abnormalities.

Ophthalmoscopy
The vitreous and optic nerve head were evaluated through a dilated pupil. Fundus pathology observations were recorded using a 5-point scale (0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe).

Cup/Disc Ratio
The cup/disc ratio was measured using direct and indirect ophthalmoscopy, and the Allergan [redacted] on a scale ranging from [redacted] Visual Field Examination: Visual field examinations (undilated) were performed using automated perimetry testing (full threshold 24-2 program), preferably with a [redacted] machine [redacted] Visual fields were reported as normal or abnormal and the mean deviation/mean defect/mean loss was recorded in decibels (dB).

Heart Rate
Heart rate was measured with patients in a resting state (seated) for at least 5 minutes. Pulse was counted over 30 seconds, multiplied by 2, and recorded in beats per minute (bpm).

Systolic and Diastolic Blood Pressure
Systolic and diastolic blood pressure were measured by a sphygmomanometer with patients in a resting state (seated) for at least 5 minutes. Blood pressure was recorded in mm Hg.

Endothelial Cell Count
At selected sites, endothelial cell density (count) was evaluated by viewing and photographing the corneal endothelium using a noncontact specular microscope. The right eye was examined first, followed by the left eye.

Table 10 - Study Design and Schedule of Assessments – Study 007

Study Visit	Time	History & Consent	Pregnancy Test	IOP	VA	BIO HR/ BP	OPH/ C/D Ratio	VF	Endothelial Cell Count	Patient Comfort/ General Inquiry	Patient Satisfaction
Prestudy	0	X		X	X	X	X	X			X
WASHOUT PERIOD (4 - 28 DAYS)[b]											
Baseline (Day 0)	0 2 7 9		X	X X X X	X	X		X	X		
PATIENTS WILL BEGIN DOSING IN THE EVENING OF THE BASELINE VISIT (BETWEEN 09:30 PM-10:30 PM)											
Week 2	0 2			X X	X	X				X	X
Week 6	0 2 7 9			X X X X	X	X				X	X
Month 3	0 2 7 9		X	X X X X	X	X	 X[c]	X	X	X	X
Month 6	0 2 7 9			X X X X	X	X		X	X	X	X
Month 9	0 2			X X	X	X				X	X
Month 1 Or Exit	0 2 7 9			X X X X	X	X	 X[d]	X	X	X	X

IOP = Intraocular Pressure; VA = Visual Acuity; BIO = Biomicroscopy; HR = Heart Rate; BP = Blood Pressure; OPH = Ophthalmoscopy; C/D = Cup/Disc; VF = Visual Field Examination (prestudy visual fields can be performed up to 6 months prior to prestudy visit. Baseline visual fields can be performed between prestudy and baseline visits.)

[a] = For those patients discontinuing from the study early and returning for office visits during their planned 12-month study period, the investigator completed a questionnaire to identify the resources used during this period.

[b] = For patients who were not going into washout, there was a minimum 2-day wait between prestudy and baseline visits.

[c] = Ophthalmoscopy should have been performed after hour 9 IOP measurement.

[d] = If the patient discontinued from the study prior to month 12 visit, all of the month 12 measurements should have been performed at the exit visit.

Reviewer's Comments:

The washout period for all drugs was in accordance with agency recommendations.

Subject Disposition and Demographics

Table 11 - Subject Disposition – Study 007

Treatment	Number of Patients Randomized (N=593)	Number of Patients Discontinued (N=74)
Brimonidine-Purite 0.15%	197	25
Brimonidine-Purite 0.2%	197	25
Alphagan	199	24

Table 12 – Discontinued Patients and Reason – Study 007

Patient	Treatment	Reason
0136-W04	Brimonidine-Purite 0.15%	Personal Reasons – hip replacement surgery
1634-B14	Brimonidine-Purite 0.15%	Adverse Events – asthenia, insomnia
1634-B34	Brimonidine-Purite 0.15%	Adverse Events – hyperemia, blurred vision, papillae
1783-U19	Brimonidine-Purite 0.15%	Adverse Events – pharyngitis
1783-U28	Brimonidine-Purite 0.15%	Adverse Events – eyelid edema, headache
1796-T01	Brimonidine-Purite 0.15%	Lack of Efficacy
1796-T17	Brimonidine-Purite 0.15%	Adverse Events – pharyngitis, oral dryness
2027-F04	Brimonidine-Purite 0.15%	Protocol violation – IOP < 22 at entry
2027-F14	Brimonidine-Purite 0.15%	Personal Reasons – Conflict with work schedule
2027-F32	Brimonidine-Purite 0.15%	Adverse Events – eye pruritus
2091-L23	Brimonidine-Purite 0.15%	Lack of Efficacy
2366-Z36	Brimonidine-Purite 0.15%	Loss to follow-up
2429-A23	Brimonidine-Purite 0.15%	Adverse Events – conjunctival hyperemia
2710-G06	Brimonidine-Purite 0.15%	Lack of Efficacy
2835-P17	Brimonidine-Purite 0.15%	Adverse Events – allergic conjuctivitis
2944-K30	Brimonidine-Purite 0.15%	Lack of Efficacy
2973-N13	Brimonidine-Purite 0.15%	Lack of Efficacy
2973-N18	Brimonidine-Purite 0.15%	Adverse Events – burning and stinging
2973-N23	Brimonidine-Purite 0.15%	Lack of Efficacy
2973-N24	Brimonidine-Purite 0.15%	Lack of Efficacy
2973-N25	Brimonidine-Purite 0.15%	Lack of Efficacy
2975-V03	Brimonidine-Purite 0.15%	Lost to follow-up
2977-D13	Brimonidine-Purite 0.15%	Adverse Events – burning, pruritis
3047-E03	Brimonidine-Purite 0.15%	Protocal violoation – alcoholism
3047-E13	Brimonidine-Purite 0.15%	Adverse Events – allergic reaction
1183-J20	Brimonidine-Purite 0.2%	Personal Reasons - asthma
1634-B19	Brimonidine-Purite 0.2%	Personal Reasons – head trauma, myalgia, syncope
1634-B20	Brimonidine-Purite 0.2%	Adverse Events – allergic conjunctivitis
1634-B41	Brimonidine-Purite 0.2%	Adverse Events – eyelid edema, asthenia, headache
1796-T03	Brimonidine-Purite 0.2%	Adverse Events – anxiety, nausea, dizziness
2027-F02	Brimonidine-Purite 0.2%	Improper Entry
2027-F06	Brimonidine-Purite 0.2%	Adverse Events – headache, eye pain, decreased libido

2027-F15	Brimonidine-Purite 0.2%	Protocol violation - alcoholism
2027-F20	Brimonidine-Purite 0.2%	Adverse Events – eyelid edema, pruritus, conjunctival edema
2091-L14	Brimonidine-Purite 0.2%	Lack of Efficacy
2091-L26	Brimonidine-Purite 0.2%	Adverse Events – conjunctival hyperemia, pruritus
2366-Z30	Brimonidine-Purite 0.2%	Improper Entry
2429-A33	Brimonidine-Purite 0.2%	Adverse Events – allergic conjunctivitis
2707-S04	Brimonidine-Purite 0.2%	Adverse Events – allergic conjunctivitis
2707-S10	Brimonidine-Purite 0.2%	Adverse Events – allergic conjunctivitis
2707-S38	Brimonidine-Purite 0.2%	Lack of Efficacy
2710-G15	Brimonidine-Purite 0.2%	Improper Entry
2944-K12	Brimonidine-Purite 0.2%	Adverse Events - folliculosis
2973-N02	Brimonidine-Purite 0.2%	Adverse Events - glossitis
2973-N17	Brimonidine-Purite 0.2%	Lack of Efficacy
2973-N27	Brimonidine-Purite 0.2%	Adverse Events – allergic conjunctivitis
2975-V35	Brimonidine-Purite 0.2%	Adverse Events – allergic conjuctivitis
2976-X01	Brimonidine-Purite 0.2%	Personal Reasons – blurry vision
2977-D15	Brimonidine-Purite 0.2%	Personal Reasons
2977-D16	Brimonidine-Purite 0.2%	Adverse Events – visual disturbance
1183-J05	ALPHAGAN	Adverse Events – myocardial infarction
1783-U04	ALPHAGAN	Adverse Events – eye pain, foreign body, oral dryness
1783-U12	ALPHAGAN	Lost to follow-up
1796-T04	ALPHAGAN	Adverse Events – hyperemia, pruritus
1796-T09	ALPHAGAN	Adverse Events – epiphora, discharge, hyperemia
1819-Y01	ALPHAGAN	Adverse Events – allergic conjuctivitis
1819-Y14	ALPHAGAN	Adverse Events – allergic conjuctivitis
2027-F10	ALPHAGAN	Adverse Events – hyperemia, pruritus
2027-F18	ALPHAGAN	Adverse Events - asthenopia
2027-F27	ALPHAGAN	Adverse Events – asthenia, stinging, visual disturbance
2429-A10	ALPHAGAN	Adverse Events – allergic conjunctivitis
2707-S42	ALPHAGAN	Adverse Events – allergic conjunctivitis
2710-G30	ALPHAGAN	Lack of Efficacy
2944-K23	ALPHAGAN	Lack of Efficacy
2944-K32	ALPHAGAN	Lack of Efficacy
2973-N05	ALPHAGAN	Adverse Events – allergic reaction
2973-N12	ALPHAGAN	Adverse Events – allergic conjunctivitis
2973-N26	ALPHAGAN	Adverse Events – allergic conjunctivitis
2975-V13	ALPHAGAN	Personal Reasons
2985-H01	ALPHAGAN	Adverse Events – elevated IOP, hyperemia, erythema
2985-H02	ALPHAGAN	Adverse Events – allergic conjunctivitis
2985-H13	ALPHAGAN	Adverse Events – allergic conjunctivitis
2986-R05	ALPHAGAN	Adverse Events – erythemia, edema, hyperemia
3047-E09	ALPHAGAN	Adverse Events – allergic conjunctivitis

Reviewers Comments: *There were significantly more patients in the 0.15% group who were discontinued due to lack of efficacy than the 0.2% group and the Alphagan group.*

Demographics

Table 13 - Demographics (Intent-to-Treat) – Study 007

		[illegible]	[illegible]	ALPHAGAN [illegible]	[illegible]
Age	Mean	62.1	61.4	60.8	0.608[a]
	Std	13.3	12.4	13.0	
	Min	28.6	25.4	25.2	
	Max	87.2	87.7	93.4	
Age group					
< 45	N	21(10.7%)	22(11.2%)	21(10.6%)	
45 - 65	N	95 (48.2%)	91(46.2%)	93(46.7%)	
> 65	N	81 (41.1%)	84(42.6%)	85(42.7%)	
Sex					0.300
Male	N	93(47.2%)	78(39.6%)	89(44.7%)	
Female	N	104(52.8%)	119(60.4%)	110(55.3%)	
Race					0.371
Caucasian	N	148(75.1%)	143(72.6%)	148(74.4%)	
Black	N	28(14.2%)	38(19.3%)	31(15.6%)	
Asian	N	0	1(0.5%)	3(1.5%)	
Hispanic	N	21(10.7%)	14(7.1%)	16(8.0%)	
Other	N	0	1(0.5%)	1(0.5%)	
Iris Color					0.542
Blue	N	61(31.0%)	56(28.4%)	53(26.6%)	
Brown	N	94(47.7%)	103(52.3%)	105(52.8%)	
Green	N	14(7.1%)	12(6.1%)	13(6.5%)	
Hazel	N	25(12.7%)	26(13.2%)	27(13.6%)	
Other	N	3(1.5%)	0	1(0.5%)	
Light		103(52.3%)	94(47.7%)	94(47.2%)	
Dark		94(47.7%)	103(52.3%)	105(52.8%)	

Reviewers Comments:

There were no statistical significant differences in demographics between the treatment groups.

Efficacy Analysis – Protocol 190342-007 (intent-to-treat population)

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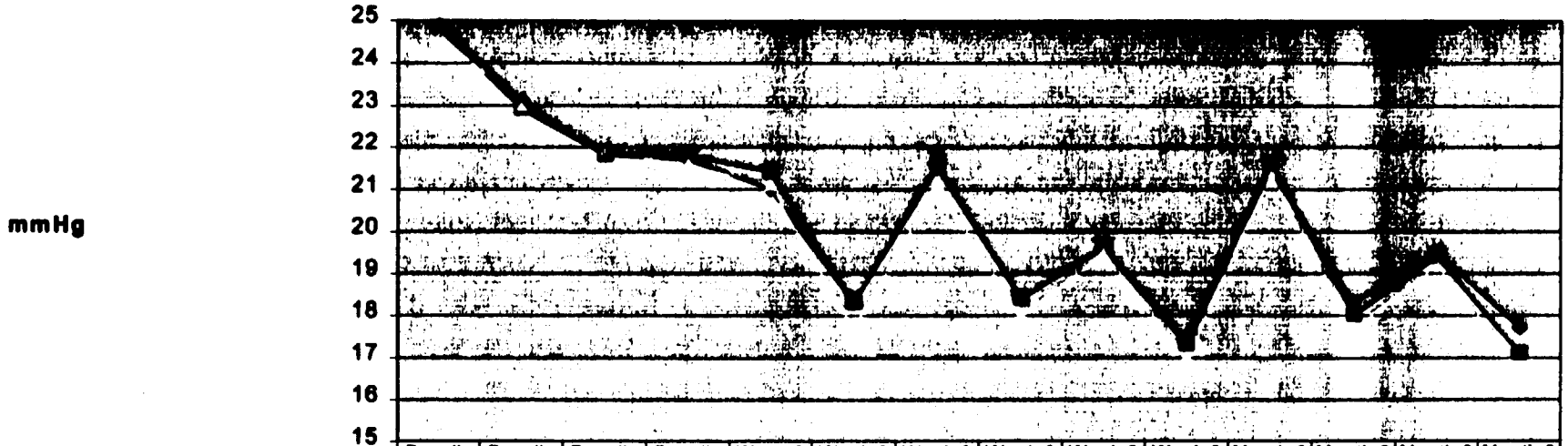
- Efficacy Variables

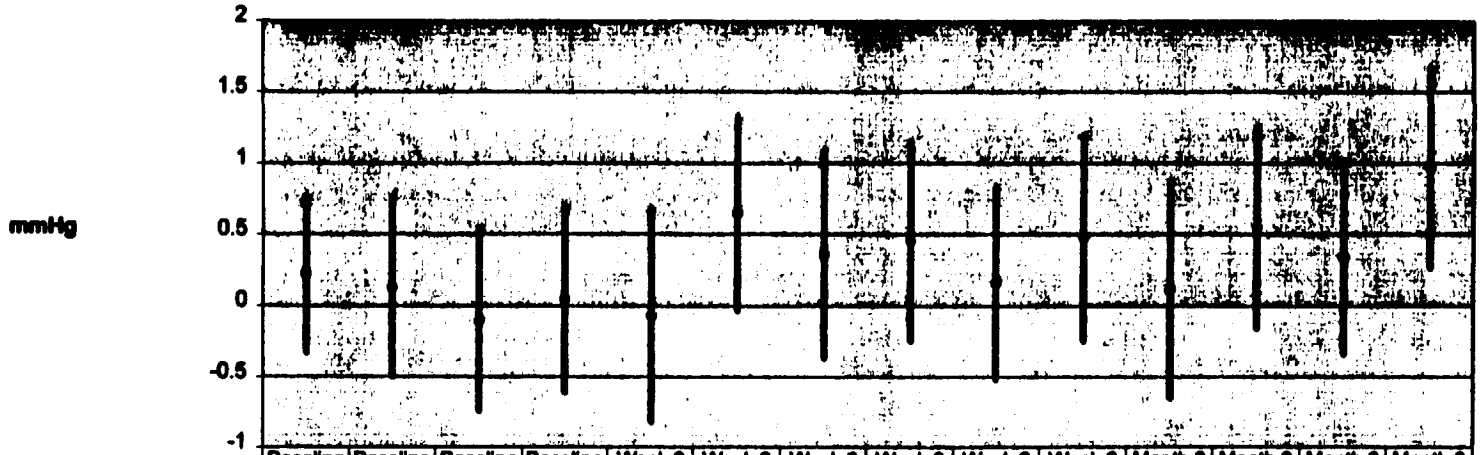
Mean Diurnal IOP - Study 007



	Baselin e (hr 0)	Baselin e (hr 2)	Baselin e (hr 7)	Baselin e (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Brimonidine-Purite 0.15%	24.9	23.1	21.8	21.7	21	18.3	21.5	18.4	19.6	17.4	21.5	18.3	19.5	17.7
Brimonidine-Purite 0.2%	24.8	22.9	21.8	21.8	21.4	18.3	21.6	18.4	19.6	17.3	21.6	18	19.4	17.1
ALPHAGAN	24.7	23	21.9	21.6	21.1	17.7	21.1	18	19.5	17	21.4	17.7	19.2	16.8

Reviewer' Comments: *There is no clinical difference between the IOP lowering effect of Brimonidine-Purite 0.15% , Brimonidine-Purite 0.2% and Alphagan for the majority of timepoints. All treatment groups failed to consistently lower IOP by 20% at trough.*

Mean Difference (Brimonidine Purite 0.15% - ALPHAGAN) with 95% Confidence Intervals - Study 007



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.33	-0.5	-0.74	-0.61	-0.82	-0.04	-0.37	-0.25	-0.52	-0.25	-0.65	-0.16	-0.34	0.26
Upper CI	0.75	0.75	0.52	0.68	0.66	1.31	1.08	1.14	0.82	1.18	0.86	1.24	1	1.66
Mean Difference	0.21	0.12	-0.11	0.04	-0.08	0.64	0.35	0.45	0.15	0.47	0.1	0.54	0.33	0.96

Reviewer's Comments: *The mean difference with 95% confidence limits in IOP lowering ability between the 0.15% group and the Alphagan group is less than 1.5 mmHg for the majority of timepoints.*

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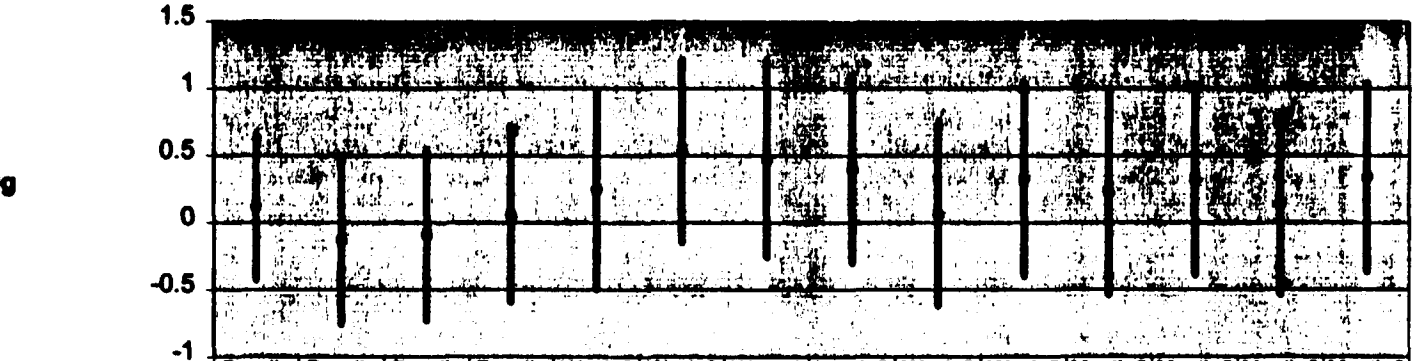
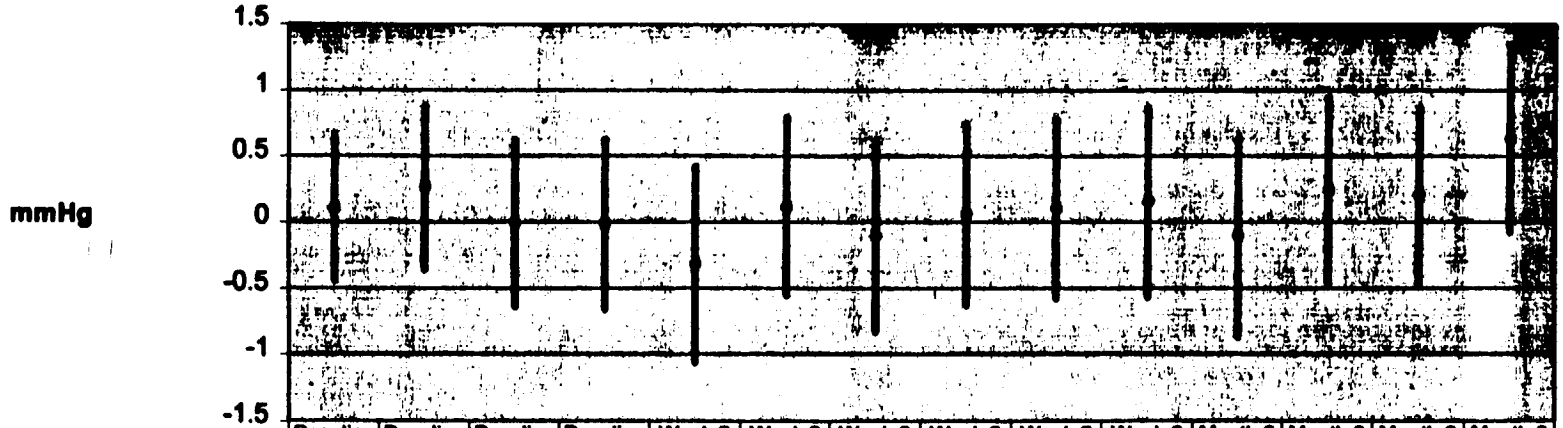
Mean Difference (Brimonidine Purite 0.2% - ALPHAGAN) with 95% Confidence Intervals - Study 007



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.43	-0.76	-0.73	-0.59	-0.5	-0.15	-0.26	-0.3	-0.62	-0.4	-0.54	-0.39	-0.54	-0.37
Upper CI	0.65	0.48	0.53	0.7	0.98	1.2	1.19	1.08	0.72	1.03	0.97	1.01	0.79	1.03
Mean Difference	0.11	-0.14	-0.1	0.05	0.24	0.52	0.46	0.39	0.05	0.32	0.22	0.31	0.13	0.33

Reviewer's Comments: *The mean difference with 95% confidence limits in IOP lowering ability between the Brimonidine Purite 0.2% group and the ALPHAGAN group is less than 1.5 mmHg for all timepoints.*

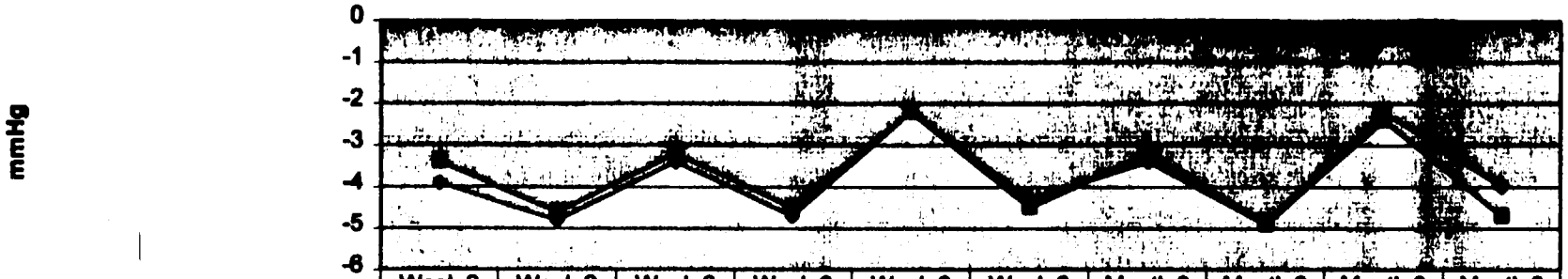
Mean Difference (Brimonidine Purite 0.15% - Brimonidine Purite 0.2%) with 95% Confidence Intervals - Study 007



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.44	-0.36	-0.64	-0.66	-1.06	-0.56	-0.63	-0.63	-0.58	-0.57	-0.67	-0.46	-0.47	-0.06
Upper CI	0.65	0.88	0.62	0.63	0.42	0.79	0.62	0.75	0.77	0.87	0.64	0.94	0.87	1.33
• Mean Difference	0.1	0.26	-0.01	-0.02	-0.32	0.11	-0.11	0.06	0.1	0.15	-0.11	0.24	0.2	0.63

Reviewer's Comments: *The mean difference with 95% confidence limits in IOP lowering ability between the 0.15% group and the 0.2% group is less than 1.5 mmHg for all timepoints.*

Mean Change in IOP from Baseline - Study 007



	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Brimonidine-Purite 0.15%	-3.9	-4.8	-3.4	-4.7	-2.2	-4.3	-3.4	-4.9	-2.2	-4
Brimonidine-Purite 0.2%	-3.4	-4.6	-3.2	-4.5	-2.2	-4.5	-3.2	-4.9	-2.4	-4.7

Reviewer' Comments: *The average IOP lowering capability of Brmonidine-Purite 0.15% and 0.2% over 3 months ranges from approximately 2mmHg to 5mmHg.*

Safety

Adverse Events

Adverse events were reported for 49.5% (97/196) of patients treated with Brimonidine-Purite 0.15%, 53.8% (106/197) of patients treated with Brimonidine-Purite 0.2%, and 56.8% (113/199) of patients treated with ALPHAGAN . ($p = 0.344$) Overall, the most frequently reported adverse events (reported by > 5% of patients in any one treatment group) in descending order were conjunctival hyperemia, visual disturbance, oral dryness, eye pruritus, burning sensation in the eye, allergic conjunctivitis, infection, and eye dryness.

Serious adverse events were reported for 2.6% (5/196) of patients receiving Brimonidine-Purite 0.15%, 0.5% (1/197) of patients receiving Brimonidine-Purite 0.2%, and 1.0% (2/199) of patients receiving ALPHAGAN ($p=0.188$).

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ON ORIGINAL

Table 14 - Number(%) of Patients with Adverse Events Reported by ≥ 2% of Patients in Any 1 Treatment Group – Study 007

Preferred Term[a]	Brimonidine-Purite™ 0.15% N=196		Brimonidine-Purite™ 0.2% N=197		ALPHAGAN® N=199		Among-group P-value[b]
Conjunctival hyperemia	16	(8.2%)	19	(9.6%)	24	(12.1%)	0.426
Visual disturbance	12	(6.1%)	17	(8.6%)	9	(4.5%)	0.244
Infection	10	(5.1%)	4	(2.0%)	9	(4.5%)	0.246
Oral dryness	10	(5.1%)	13	(6.6%)	13	(6.5%)	0.782
Burning sensation in eye	8	(4.1%)	6	(3.0%)	10	(5.0%)	0.607
Eye pruritus	6	(3.1%)	16	(8.1%)	11	(5.5%)	0.092
Asthenia	5	(2.6%)	4	(2.0%)	9	(4.5%)	0.313
Eye dryness	5	(2.6%)	10	(5.1%)	8	(4.0%)	0.429
Infection sinus	5	(2.6%)	0	(0.0%)	3	(1.5%)	0.073
Pharyngitis	5	(2.6%)	3	(1.5%)	1	(0.5%)	0.186
Arthritis	4	(2.0%)	2	(1.0%)	2	(1.0%)	0.611
Flu syndrome	4	(2.0%)	2	(1.0%)	4	(2.0%)	0.729
Headache	4	(2.0%)	5	(2.5%)	4	(2.0%)	0.942
Photophobia	4	(2.0%)	0	(0.0%)	2	(1.0%)	0.112
Stinging sensation in eye	4	(2.0%)	0	(0.0%)	4	(2.0%)	0.128
Allergic conjunctivitis	3	(1.5%)	8	(4.1%)	13	(6.5%)	0.042[c]
Blepharitis	3	(1.5%)	0	(0.0%)	2	(1.0%)	0.255
Epiphora	3	(1.5%)	3	(1.5%)	6	(3.0%)	0.616
Foreign body sensation	3	(1.5%)	4	(2.0%)	8	(4.0%)	0.342
Hypertension	3	(1.5%)	3	(1.5%)	6	(3.0%)	0.616
Visual acuity worsened	3	(1.5%)	4	(2.0%)	3	(1.5%)	0.927
Conjunctival folliculosis	2	(1.0%)	6	(3.0%)	3	(1.5%)	0.353
Eye discharge	2	(1.0%)	3	(1.5%)	5	(2.5%)	0.622
Eyelid edema	2	(1.0%)	4	(2.0%)	4	(2.0%)	0.783
Eye pain	1	(0.5%)	4	(2.0%)	7	(3.5%)	0.110
Somnolence	1	(0.5%)	4	(2.0%)	4	(2.0%)	0.410
Dizziness	0	(0.0%)	6	(3.0%)	2	(1.0%)	0.024[d]
Rash	0	(0.0%)	4	(2.0%)	1	(0.5%)	0.092

a Adverse events presented in decreasing frequency of reports in the Brimonidine-Purite™ 0.15% group.

b Among-group p-value based on the Fisher's exact test or the Pearson's chi-square test.

c Statistically significant difference between Brimonidine-Purite™ 0.15% and ALPHAGAN® (p = 0.012).

d Statistically significant difference between Brimonidine-Purite™ 0.15% and Brimonidine-Purite™ 0.2% (p = 0.030)

Reviewer's Comments: *The adverse event profile of Brimonidine-Purite 0.15% and Alphagan are similar with the exception of allergic conjunctivitis being statistically significantly more in the Alphagan group. Conjunctival hyperemia, pruritis and conjunctival folliculosis may all be forms of allergic conjunctivitis.*

Table 15- Serious Adverse Events – Study 007

Patient Number	Treatment	Adverse Event	Outcome	Discontinued from Study
1796-T24	Brimonidine-Purite 0.15%	Arm Pain	Recovered w/o sequele	No
2091-L17	Brimonidine-Purite 0.15%	Myocardial Infarction	Recovered w/o sequele	No
2429-A13	Brimonidine-Purite 0.15%	Kidney Calculus	Recovered w/o sequele	No
2975-V07	Brimonidine-Purite 0.15%	Overdose	Recovered w/o sequele	No
3047-E03	Brimonidine-Purite 0.15%	Alcohol Intolerance	Recovered w/ sequele	No
1796-T13	Brimonidine-Purite 0.2%	Right Heart Failure	Ongoing	No
1183-J05	Alphagan	Myocardial Infarction	Recovered w/ sequele	Yes
2944-K20	Alphagan	Right Heart Failure	Recovered w/o sequele	No

Reviewer's Comments: *Per case report form, patient 2975-V07 underwent a voluntary hysterectomy as preventive treatment for possible side effects of Tamoxifen which may include cervical cancer.*

Visual Acuity

For visual acuity, all analyses were performed on the eye with the most unfavorable change from baseline as this was the most conservative evaluation. At the final visit, there were no significant differences among the treatment groups

Table 16 - Visual Acuity Change from Baseline – Study 007

Visual Acuity Change (Lines)	Brimonidine-Purite 0.15% (N=196)	Brimonidine-Purite 0.2% (N=197)	ALPHAGAN (N=199)
≤ -2	16 (8.2%)	23 (11.7%)	22 (11.1%)
> -2 to ≤ -1	52 (26.8%)	55 (28.1%)	36 (18.2%)
> -1 to < 0	20 (10.3%)	23 (11.7%)	21 (10.6%)
0	81 (41.8%)	74 (37.8%)	88 (44.4%)
> 0 to < 1	9 (4.6%)	10 (5.1%)	8 (4.0%)
≥ 1 to < 2	14 (7.2%)	8 (4.1%)	16 8.1%)
≥ 2	1 (1.0%)	3 (1.5%)	7 (3.5%)

Reviewers comments:. *The among group differences in the worsening of visual acuity by ≥ 2 lines were not statistically significant.*

Cup-Disc Ratio

For cup/disc ratio, the analysis was performed on the eye with the most unfavorable change from baseline. A similar pattern of distribution of worst change from baseline in cup/disc ratio at month 3 was seen among the 3 treatment groups.

Table 17- Cup-Disc Ratio Change from Baseline at Month 3 – Study 007

Cup-Disc Ratio Change from Baseline	Brimonidine-Purite 0.15% (N=196)	Brimonidine-Purite 0.2% (N=197)	ALPHAGAN (N=199)
≤ -0.2	2 (1.1%)	3 (1.6%)	1 (0.5%)
> -0.2 to ≤ -0.1	4 (2.1%)	2 (1.1%)	6 (3.1%)
> -0.1 to < 0	3 (1.6%)	2 (1.1%)	2 (1.0%)
0	165 (87.8%)	159 (83.7%)	172 (88.7%)
> 0 to < 0.1	4 (2.1%)	16 (8.4%)	4 (2.1%)
≥ 0.1 to < 0. 2	6 (3.2%)	7 (3.7%)	6 (3.1%)
≥ 0.2	4 (2.1%)	1 (0.5%)	3 (1.5%)

Endothelial Cell Count

The endothelial cell count analyses was performed on the eye with the most unfavorable change from baseline. Endothelial cell count data were collected at 9 sites in a total of 242 patients. There was no statistically significant difference among treatment groups in endothelial cell count at baseline or the change from baseline at month 3 ($p \geq 0.281$). The within-group mean decreases from baseline in endothelial cell count were 34 cells in the 0.15% group (p=0.285), 25.9 cells in the 0.2% group (p=0.447), and 13.8 cells in the Alphagan group (p=0.662).

Table 18 - Mean Endothelial Cell Count – Study 007

	Brimonidine-Purite 0.15%	**Brimonidine-Purite 0.2%**	**Alphagan**
Baseline	2385.6	2387.3	2465.0
Month 3	2351.6	2361.4	2451.2

Reviewer's Comments: *There were no clinically significant changes in endothelial cell count between baseline and 3 months in any of the treatment groups.*

Heart rate/ Blood Pressure

Reviewers Comments:
There were no clinically significant changes in heart rate or blood pressure in any of the treatments groups at any point throughout the study.

Reviewer's Summary of Safety and Efficacy

Brimonidine-Purite 0.15% and 0.2% have similar IOP lowering ability.

The average IOP lowering capability of Brimonidine-Purite 0.15% and 0.2% ranges from approximately 2mmHg to 5mmHg.

The adverse event profile of Brimonidine 0.15% is similar to Alphagan with exception of allergic conjunctivitis which is statistically higher with Alphagan.

8.3 **Study #3 Protocol 190342-008**

Title: Same as Protocol 190342-007

Objective: Same as Protocol 190342-007

Study Design: Same as Protocol 190342-007

Test Drug Schedule: Same as Protocol 190342-007

Table 19 - Clinical Sites – Study 008

Principal Investigator Name (Number), Address	Subinvestigator	Number of Subjects Enrolled	Subject ID Serie
Mark Abelson, M.D. (1584) 863 Turnpike Street, Suite 224 North Andover, MA 01845	Terry Chin, O.D. Jack Greiner, O.D., D.O., Ph.D. Kathleen Krenzer, O.D., Ph.D. Charles Leahy, O.D. H. Jerome Cranton, M.D. Gerald Spindel, M.D. Bernard Heersink, M.D. Diane Risco, O.D. Nabeel Jarudi, M.D. John Pietriantonio, O.D. Timothy Jordan, O.D. Douglas Blair, O.D. James Lenhart, O.D.	37	A01-A37
Edward Andersen, M.D. (2972) 283 Pond Street Woonsocket, RI, 02895	Thomas Lang, M.D.	38	U01-U38
Jon Dietlein, M.D. (2974) San Gabriel Eye Center 950 W. University, Suite 108 Georgetown, TX 78626	Jomes Montgomery, M.D.	33	B51-B83
Harvey DuBiner, M.D. (2450) Clayton Eye Center 1000 Corporate Center Drive, Suite 100 Morrow, GA 30260		40	S01-S40
L. Jay Katz, M.D. (1960) Spaeth/Katz, PC Wills Eye Hospital 900 Walnut St. Philadelphia, PA 19107	George Spaeth, M.D. Jonathan Myers, M.D. Richard Wilson, M.D. Marlene Moster, M.D. Court Schmidt, M.D. Richard Hulzen, M.D. Asher Weiner, M.D. Helen Danesh-Meyer, M.D. Jeff Henderer Karl Siebert, M.D. Erkan Mutlukan, M.D.	8	Y01-Y08

Alex Kent, M.D. (2980) Dept. of Ophthalmology Medical University of South Carolina 171 Ashley Avenue Charleston, S.C. 29425-2236	Lisa Langdale, R.N.	43	W01-W43
Jeff Lozier, M.D. (2981) Centre for Health Care Medical Associates 10865 Rancho Bernardo Rd. San Diego, CA 92127	Belinda Dure-Smith, M.D. Margaret Drehobl, M.D. Linda Skific, RNP	31	N01-N31
Jeffrey Morris, M.D. (2122) 477 N. El Camino Real, #C 202 Encinitas, CA 92024 3909 Waring Rd., Suite B Oceanside, CA 92056	Larry Rice, M.D. Janie Bodman, O.D. Chantelle Clarizio, O.D.	48	T01-T48
Thomas Mundorf, M.D. (1485) Prebyterian Medical Tower 1718 E. 4th Street, Suite 806 Charlotte, NC 28204		31	B01-B31
Matthew Parsons, M.D. (2983) Western Research Alliance 131 West 500 South, PMB 411 Bountiful, UT 84010	David Brodstein, M.D. Bradley Richards, M.D. Scott Richards, M.D.	35	E01-E35
Jay Perlman, M.D., Ph.D. (2987) Department of Veterans Affairs Edward Hines, Jr. Hospital Roosevelt & First Streets Hines, IL 60141	Geoffrey Emerick, M.D. Anuradha Khanna, M.D.	13	A51-A59 A61-A64
Arnold Prywes, M.D. (2893) Glaucoma Consultants of Long Island Eye Care Associates 4212 Hempstead Turnpike Bethpage, NY 11714	Craig Marcus, M.D.	17	F01-F11 F13-F18
Patrick Riedel, M.D. (2984) Bend Memorial Clinic 1501 NE Medical Center Dr. Bend, OR 97701	Patricia Buehler, M.D. Robert Mathews, M.D. Nancy Bonetto, OD Janer Wilkerson, CCRC, Mgr.	30	C01-C30
Thomas Samuelson, M.D. (2161) Minnesota Eye Consultants 710 East 24 th Street, Suite 106 Minneapolis, MN 55404	Elizabeth Davis, M.D. Eric Linebarger, M.D. Liz Davies	7	L01-L07
Steven Simmons, M.D. (1655) Center For Sight 349 Northern Blvd. Albany, NY	Martin Kaback, M.D. Michael Moore, M.D.	17	J01-J17
Richard Sturm, M.D. (1587) 200 Hempstead Ave. Lynbrook, NY 11563	Ronald Caronia, M.D. Stanley Berke, M.D. Barbara Burger, RN	44	H01-H44
Stuart Terry, M.D. (1512) Braverman-Terry Eye Associate 1100 North Main Avenue San Antonia, TX 78212	Sheldon Braverman, M.D. Thomas Oei, M.D.	28	D01-D28
Christopher Tortora, M.D. (2026) Hawaiian Eye Center 606 Kilani Avenue Wahiawa, HI 96786-1993	Bruce Ballon, M.D. Douglas Chu, M.D.	6	M01-M06

Mark Weiss, M.D. (0642) Keystone Research 1717 South Utica, Suite 107 Tulsa, OK 74104		8	Z01-Z08
Sidney Weiss, M.D. (0565) 27800 Medical Center Road Suite 130 Mission Viejo, CA 92691	William Berger, M.D. Luis Channes, M.D. Mark Sugar, M.D. J. Ellen Schonfeld, RN, MN, CNP Janis Davidson, RN, MSN, CPNP	18	X01-X18
Eugene Wolchok, M.D. (2988) Jacksonville Center for Clinical Research 4004 University Blvd. South Jacksonville, FL 32215	Anil Mahajan, M.D. Michael Koren, M.D.	21	R01-R21

Study Design

Identical to Study 007

Subject Disposition and Demographics

Disposition

Table 20 - Subject Disposition – Study 008

Treatment	Number of Patients Randomized (N=554)	Number of Patients Discontinued (N=71)
Brimonidine-Purite 0.15%	184	24
Brimonidine-Purite 0.2%	186	27
Alphagan	184	20

Table 21 – Discontinued Patients and Reason – Study 008

Patient	Treatment	Reason
0642-Z04	Bromonidine-Purite 0.15%	Adverse Events – blurred vision
0642-Z06	Bromonidine-Purite 0.15%	Investigator Withdrawal from Study
0642-Z08	Bromonidine-Purite 0.15%	Investigator Withdrawal from Study
1485-B05	Bromonidine-Purite 0.15%	Lack of Efficacy
1485-B07	Bromonidine-Purite 0.15%	Lack of Efficacy
1512-D07	Bromonidine-Purite 0.15%	Adverse Events – allergic reaction
1584-A04	Bromonidine-Purite 0.15%	Adverse Events – pruritus

1584-A06	Bromonidine-Purite 0.15%	Lack of Efficacy
1587-H35	Bromonidine-Purite 0.15%	Adverse Events – change in near vision
2026-M01	Bromonidine-Purite 0.15%	Adverse Events – headaches, blurred vision
2161-L06	Bromonidine-Purite 0.15%	Adverse Events - conjunctivitis
2450-S13	Bromonidine-Purite 0.15%	Adverse Events – photophobia, corneal erosion
2450-S29	Bromonidine-Purite 0.15%	Lack of Efficacy
2893-F09	Bromonidine-Purite 0.15%	Personal Reasons
2972-U01	Bromonidine-Purite 0.15%	Adverse Events – hyperemia, prutitis
2972-U34	Bromonidine-Purite 0.15%	Prohibited Medication-Toprol XL 50 mg
2974-B63	Bromonidine-Purite 0.15%	Adverse Events – allergic conjunctivitis
2974-B77	Bromonidine-Purite 0.15%	Lack of Efficacy
2974-B80	Bromonidine-Purite 0.15%	Lack of Efficacy
2980-W04	Bromonidine-Purite 0.15%	Lack of Efficacy
2980-W30	Bromonidine-Purite 0.15%	Non-compliance
2983-E34	Bromonidine-Purite 0.15%	Adverse Events – conjunctivitis
2984-C10	Bromonidine-Purite 0.15%	Adverse Events – atopic dermatitis
2984-C17	Bromonidine-Purite 0.15%	Adverse Events - conjunctivitis
0642-Z01	Brimonidie-Purite 0.2%	Lack of Efficacy
0642-Z03	Brimonidie-Purite 0.2%	Investigator withdrawal from study
1485-B01	Brimonidie-Purite 0.2%	Lack of Efficacy
1485-B02	Brimonidie-Purite 0.2%	Lack of Efficacy
1485-B10	Brimonidie-Purite 0.2%	Lack of Efficacy
1485-B11	Brimonidie-Purite 0.2%	Lack of Efficacy
1584-A21	Brimonidie-Purite 0.2%	Adverse Events – itching, erythema
1584-A34	Brimonidie-Purite 0.2%	Prohibited medication- metoprolol
1587-H13	Brimonidie-Purite 0.2%	Other- cataract removal required for profession
1655-J10	Brimonidie-Purite 0.2%	Adverse Events – allergic conjunctivitis
2122-T03	Brimonidie-Purite 0.2%	Adverse Events – itching, injection
2122-T05	Brimonidie-Purite 0.2%	Adverse Events – itching, injection, lid edema
2122-T21	Brimonidie-Purite 0.2%	Adverse Events – cerebral vascular accidents
2122-T44	Brimonidie-Purite 0.2%	Adverse Events – blurred vision
2450-S02	Brimonidie-Purite 0.2%	Improper entry
2450-S15	Brimonidie-Purite 0.2%	Personal reasons – time constraints
2450-S27	Brimonidie-Purite 0.2%	Adverse Events – dry mouth, fatigue, dizziness
2972-U32	Brimonidie-Purite 0.2%	Adverse Events – dry mouth, fatigue
2974-B81	Brimonidie-Purite 0.2%	Adverse Events – allergic conjunctivitis
2980-W01	Brimonidie-Purite 0.2%	Personal Reasons
2980-W08	Brimonidie-Purite 0.2%	Improper Entry
2980-W10	Brimonidie-Purite 0.2%	Improper Entry
2981-N29	Brimonidie-Purite 0.2%	Prohibited medication
2981-N31	Brimonidie-Purite 0.2%	Adverse Events – infection, allergy
2983-E05	Brimonidie-Purite 0.2%	Adverse Events – burning, stinging, itching
2984-C02	Brimonidie-Purite 0.2%	Lost to follow-up
2984-C12	Brimonidie-Purite 0.2%	Personal reasons
0642-Z02	ALPHAGAN	Investigator Withdrawal from Study
0642-Z05	ALPHAGAN	Improper entry
0642-Z07	ALPHAGAN	Investigator Withdrawal from Study
1512-D04	ALPHAGAN	Adverse Events – blepharitis
1512-D28	ALPHAGAN	Adverse Events – hyperemia, irritation

1587-H12	ALPHAGAN	Adverse Events – Conjunctival Follicles
1587-H22	ALPHAGAN	Adverse Events – hyperemia, edema
2122-T31	ALPHAGAN	Personal reasons
2450-S01	ALPHAGAN	Improper entry
2893-F17	ALPHAGAN	Adverse events – edema, discharge
2972-U05	ALPHAGAN	Adverse events – epiphora, pruritus,edema
2974-B52	ALPHAGAN	Adverse events – Somnolence
2974-B57	ALPHAGAN	Adverse events – allergic conjunctivitis
2980-W16	ALPHAGAN	Adverse events – allergic conjunctivitis
2980-W35	ALPHAGAN	Adverse events – allergic conjunctivitis
2981-N22	ALPHAGAN	Adverse events – allergic conjunctivitis
2984-C06	ALPHAGAN	Adverse events – irritation, itch
2984-C23	ALPHAGAN	Adverse events - conjunctivitis
2987-A61	ALPHAGAN	Lack of Efficacy
2988-R21	ALPHAGAN	Adverse Events – fatigue, dry mouth

Reviewers Comments:

Significantly more patients were discontinued in the Brimonidine-Purite 0.15% and 0.2% groups due to lack of efficacy than the Alphagan group. Fifty percent of the patients discontinued in this study due to lack of efficacy were treated by investigator number 1485.

Per case report form, patient 2981-N29 was started on two systemic adrenergic agents (Flomax and Coreg) during the study which is an exclusionary criteria of this study.

Investigator number 0642 (Mark Weiss, MD), subject series Z01-Z08 voluntarily withdrew due to his inability to commit the time requirement to conduct the study.

Demographics

Table 22 - Demographics (Intent-to-Treat) – Study 008

		[illegible]	[illegible]	ALPHAGAN (N=184)	P value
Age	Mean	64.8	66.3	64.7	0.349
	Std	12.1	11.2	11.8	
	Min	22.4	37.7	30.2	
	Max	88.8	90.4	86.2	
Age group					
< 45	N	14 (7.6%)	8 (4.3%)	9 (4.9%)	
45 - 65	N	64 (34.8%)	63 (33.9%)	77 (41.8%)	
> 65	N	106 (57.6%)	115 (61.8%)	98 (53.3%)	
Sex					0.742
Male	N	76 (41.3%)	84 (45.2%)	78 (42.4%)	
Female	N	108 (58.7%)	102 (54.8%)	106 (57.6%)	
Race					0.679
Caucasian	N	155 (84.2%)	155 (83.3%)	157 (85.3%)	
Black	N	20 (10.9%)	21 (11.3%)	16 (8.7%)	
Asian	N	2 (1.1%)	0	0	
Hispanic	N	7 (3.8%)	9 (4.8%)	10 (5.4%)	
Other	N	0	1 (0.5%)	1 (0.5%)	
Iris Color					0.341
Blue	N	52 (28.3%)	52 (28%)	58 (31.5%)	
Brown	N	85 (46.2%)	93 (50%)	78 (42.4%)	
Green	N	9 (4.9%)	6 (3.2%)	5 (2.7%)	
Hazel	N	34 (18.5%)	32 (17.2%)	41 (22.3%)	
Other	N	4 (2.2%)	3 (1.6%)	2 (1.1%)	
Light		99 (53.8%)	93 (50%)	106 (57.6%)	
Dark		85 (46.2%)	93 (50%)	78 (42.4%)	

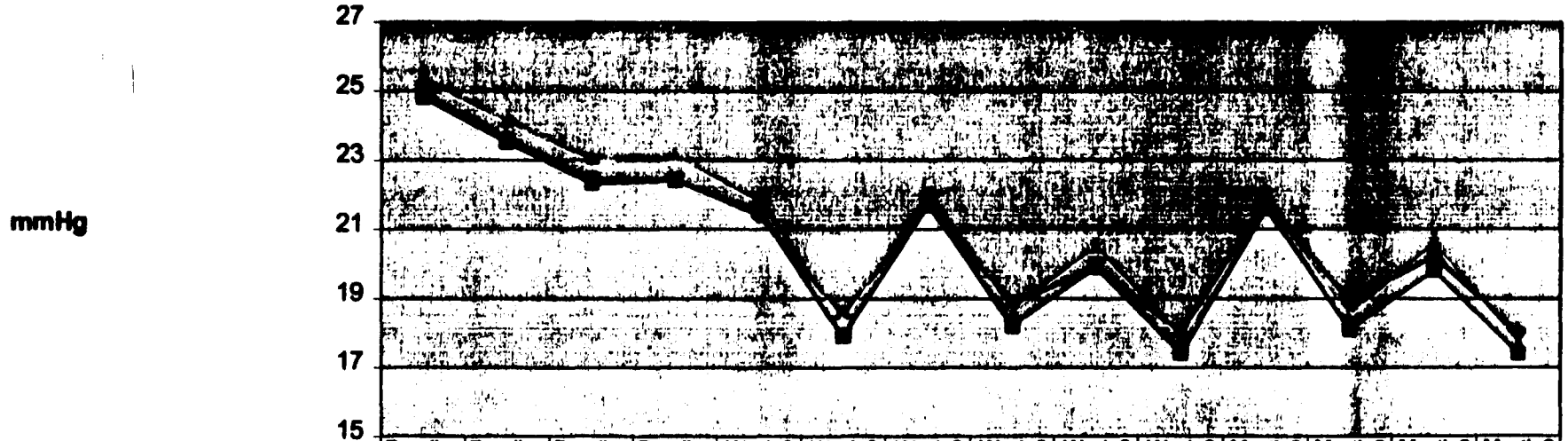
Reviewers Comments:

There were no significant differences in demographics between the treatment groups.

Efficacy Analysis – Protocol 190342-008 (intent-to-treat population)

Efficacy Variables

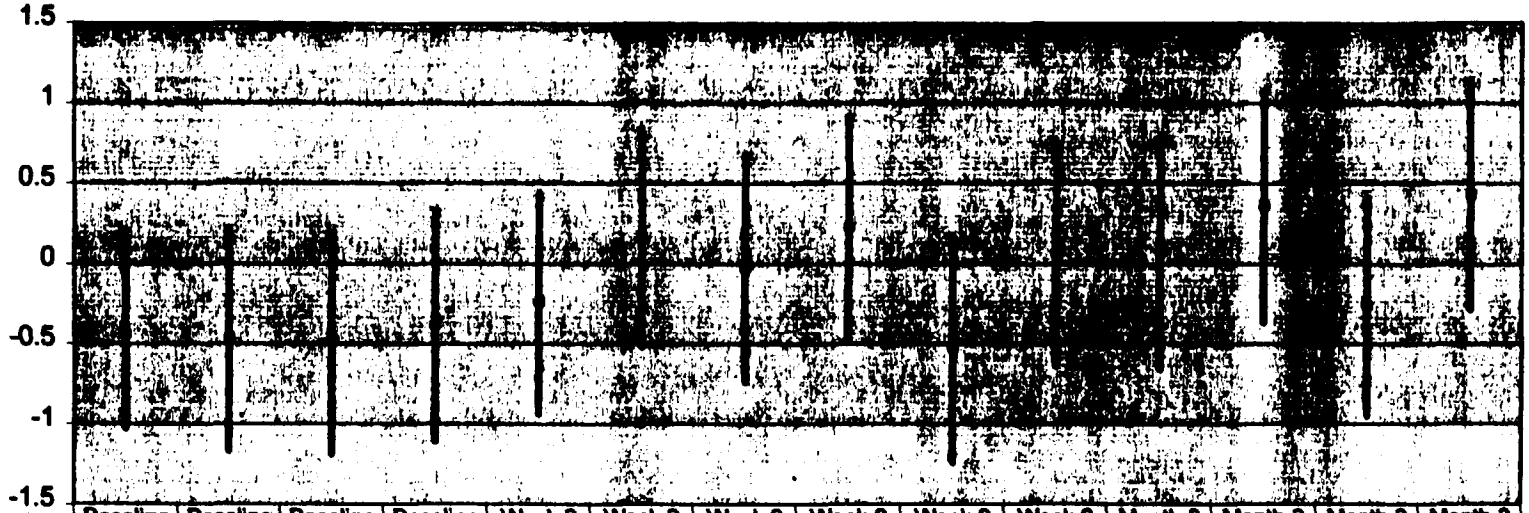
Mean Diurnal IOP - Study 008



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Brimonidine-Purite 0.15%	24.9	23.6	22.4	22.4	21.4	18.5	21.7	18.8	19.9	18	21.8	18.9	20.2	18
Brimonidine-Purite 0.2%	24.8	23.5	22.3	22.4	21.5	17.9	21.7	18.2	19.9	17.4	21.6	18.1	19.8	17.4
ALPHAGAN	25.3	24.1	23	23.1	21.8	18.4	22	18.7	20.5	17.9	21.8	18.5	20.6	17.7

Reviewer's Comments: : *There is no clinical difference between the IOP lowering effect of Brimonidine-Purite 0.15%, 0.2% and Alphagan for the majority of timepoints. All treatment groups failed to consistently lower IOP by 20% at trough*

Mean Difference (Brimonidine Purite 0.15% - ALPHAGAN) with 95% Confidence Intervals - Study 008

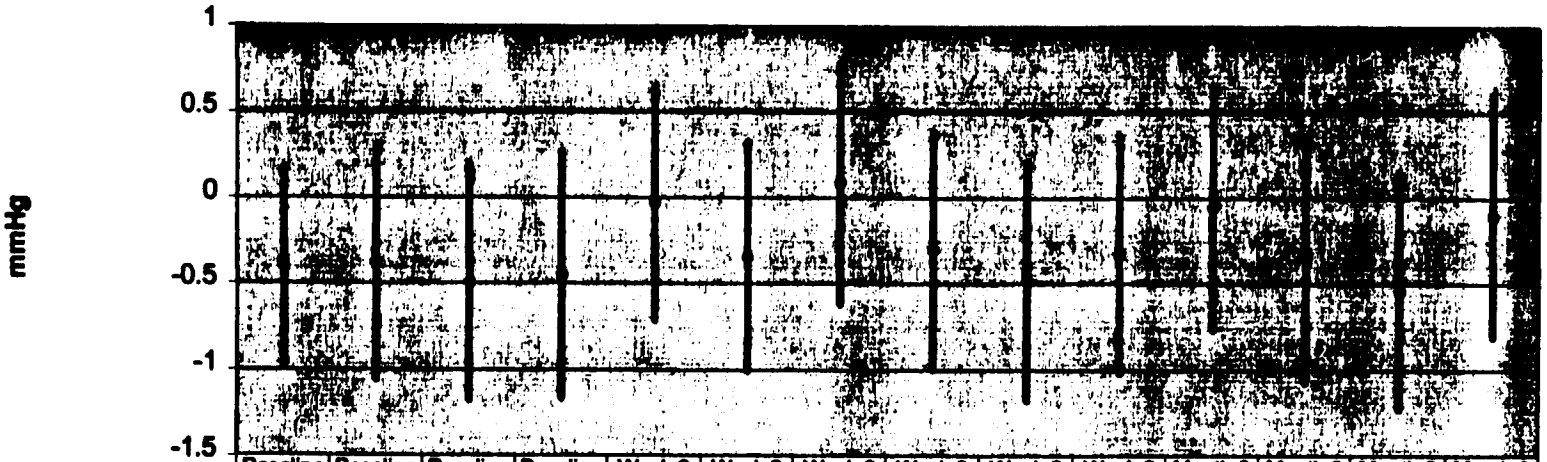


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-1.03	-1.17	-1.19	-1.11	-0.94	-0.52	-0.74	-0.48	-1.24	-0.64	-0.66	-0.37	-0.95	-0.29
Upper CI	0.13	0.2	0.18	0.32	0.43	0.83	0.67	0.91	0.18	0.74	0.78	1.07	0.41	1.13
• Mean Difference	-0.45	-0.48	-0.5	-0.39	-0.25	0.15	-0.04	0.22	-0.54	0.05	0.06	0.35	-0.27	0.42

Reviewers Comments:

The upper and lower limits of the 95% confidence intervals are within 1.5 mmHg at all timepoints for the comparision between Brimonidine-Purite 0.15% and ALPHAGAN.

Mean Difference (Brimonidine Purite 0.2% - ALPHAGAN) with 95% Confidence Intervals - Study 008

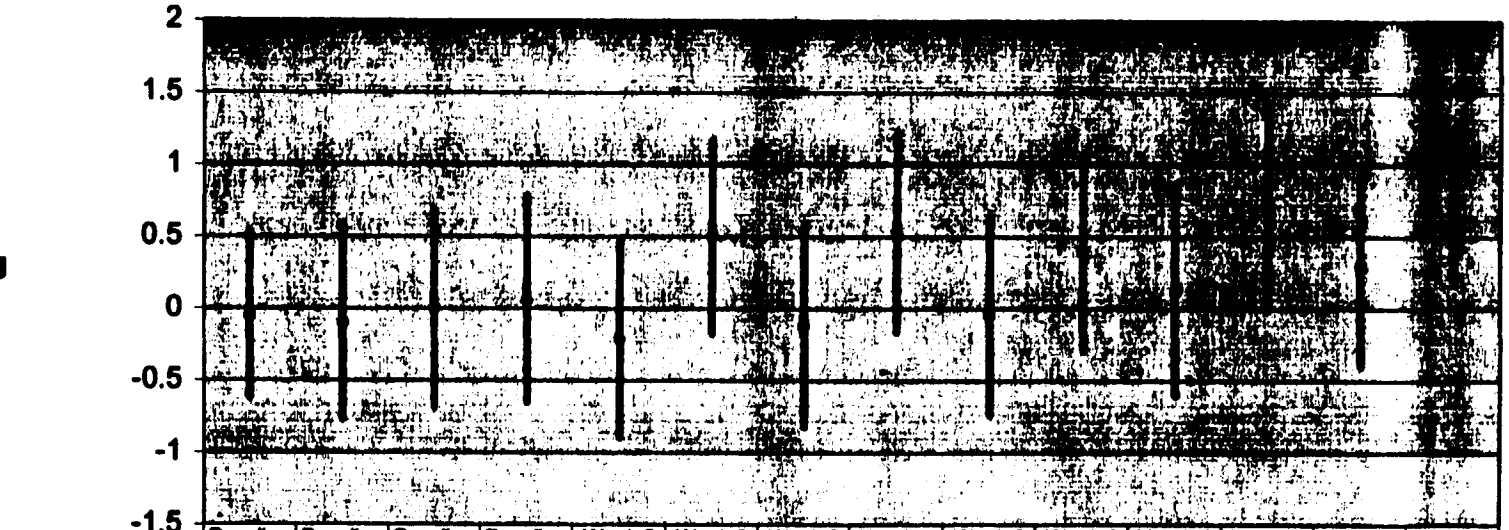


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.98	-1.06	-1.18	-1.17	-0.72	-1.01	-0.62	-1	-1.18	-1.02	-0.77	-1.07	-1.23	-0.81
Upper CI	0.17	0.29	0.18	0.26	0.64	0.32	0.78	0.38	0.2	0.35	0.65	0.36	0.12	0.6
• Mean Difference	-0.41	-0.39	-0.5	-0.46	-0.04	-0.35	0.08	-0.31	-0.49	-0.34	-0.06	-0.35	-0.55	-0.11

Reviewers Comments:

The upper and lower limits of the 95% confidence intervals are within 1.5 mmHg at all timepoints for the comparision between Brimonidine-Purite 0.2% and ALPHAGAN.

Mean Difference (Brimonidine Purite 0.15% - Brimonidine Purite 0.2%) with 95% Confidence Intervals - Study 008

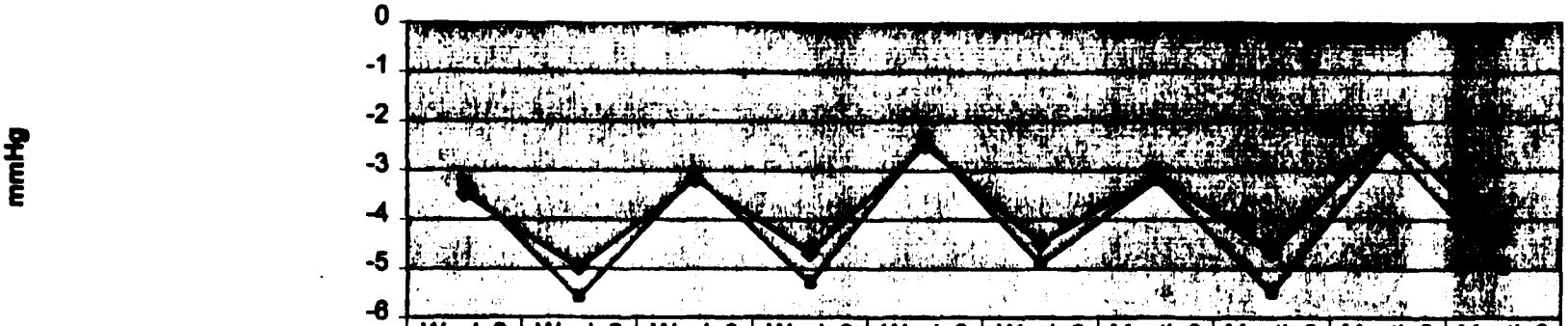


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.62	-0.77	-0.69	-0.65	-0.9	-0.17	-0.82	-0.16	-0.74	-0.29	-0.6	-0.01	-0.4	0.18
Upper CI	0.53	0.58	0.68	0.78	0.47	1.17	0.58	1.22	0.64	1.06	0.83	1.42	0.96	1.24
• Mean Difference	-0.05	-0.1	0	0.06	-0.21	0.5	-0.12	0.53	-0.05	0.39	0.12	0.7	0.28	0.53

Reviewers Comments:

The upper and lower limits of the 95% confidence intervals are within 1.5 mmHg at all timepoints for the comparision between Brimonidine-Purite 0.15% and Brimonidine-Purite 0.2%.

Mean Change in IOP from Baseline - Study 008



	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Brimonidine Purite 0.15%	-3.5	-5	-3.2	-4.7	-2.5	-4.5	-3.1	-4.7	-2.2	-4.4
Brimonidine Purite 0.2%	-3.3	-5.6	-3.1	-5.3	-2.4	-4.9	-3.2	-5.5	-2.5	-5

Reviewer' Comments: *The average IOP lowering ability of Brimonidine-Purite 0.15% over 3 months ranges from approximately The average IOP lowering ability of the 0.2% concentration is approximately*

Safety

Adverse Events

Adverse events (1 or more) were reported for 54.9% (101/184) of patients treated with Brimonidine-Purite 0.15%, 55.4% (103/186) of patients treated with Brimonidine-Purite 0.2%, and 65.2% (120/184) of patients treated with ALPHAGAN (p = 0.076) The most common adverse events in descending order of overall incidence were conjunctival hyperemia, oral dryness, visual disturbance, burning sensation in the eye, eye pruritus, infection, allergic conjunctivitis, and conjunctival folliculosis. Serious adverse events were reported for 2.7% (5/184) of patients receiving Brimonidine-Purite 0.15%, 2.7% (5/186) of patients receiving Brimonidine-Purite 0.2%, and 3.3% (6/184) of patients receiving ALPHAGAN. One death was reported during the study in the Brimonidine-Purite 0.2% group: a woman died after a cerebrovascular accident

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Table 23 – Number (%) of Patients with Adverse Events Reported by ≥ 2% of Patients in Any One Treatment Group – Study 008

[illegible]	[illegible]		[illegible]		ALPHAGAN [illegible]	[illegible]
Conjunctival hyperemia	14	(7.6%)	18	(9.7%)	21 (11.4%)	0.462
Visual disturbance	14	(7.6%)	14	(7.5%)	16 (8.7%)	0.898
Eye pruritus	11	(6.0%)	10	(5.4%)	11 (6.0%)	>0.960
Infection	9	(4.9%)	3	(1.6%)	10 (5.4%)	0.125
Burning sensation in eye	7	(3.8%)	13	(7.0%)	14 (7.6%)	0.264
Headache	6	(3.3%)	7	(3.8%)	5 (2.7%)	0.851
Oral dryness	6	(3.3%)	19	(10.2%)	22 (12.0%)	0.007
Allergic conjunctivitis	5	(2.7%)	11	(5.9%)	6 (3.3%)	0.241
Foreign body sensation	5	(2.7%)	7	(3.8%)	8 (4.3%)	0.697
Conjunctival folliculosis	4	(2.2%)	6	(3.2%)	12 (6.5%)	0.083
Cough increased	4	(2.2%)	1	(0.5%)	3 (1.6%)	0.375
Eye dryness	4	(2.2%)	5	(2.7%)	3 (1.6%)	0.933
Infection sinus	4	(2.2%)	1	(0.5%)	0 (0.0%)	0.092
Irritation eye	4	(2.2%)	3	(1.6%)	5 (2.7%)	0.720
Periodontal abscess	4	(2.2%)	2	(1.1%)	1 (0.5%)	0.418
Blepharitis	3	(1.6%)	1	(0.5%)	4 (2.2%)	0.375
Pharyngitis	3	(1.6%)	4	(2.2%)	0 (0.0%)	0.171
Asthenia	2	(1.1%)	3	(1.6%)	6 (3.3%)	0.353
Epiphora	2	(1.1%)	8	(4.3%)	6 (3.3%)	0.170
Eye pain	2	(1.1%)	5	(2.7%)	6 (3.3%)	0.414
Somnolence	2	(1.1%)	7	(3.8%)	6 (3.3%)	0.248
Dizziness	1	(0.5%)	2	(1.1%)	4 (2.2%)	0.418
Eye discharge	1	(0.5%)	2	(1.1%)	7 (3.8%)	0.077
Flu syndrome	1	(0.5%)	1	(0.5%)	4 (2.2%)	0.337
Hypertension	1	(0.5%)	3	(1.6%)	5 (2.7%)	0.262
Abnormal vision NOS	0	(0.0%)	0	(0.0%)	4 (2.2%)	0.024

Adverse events resulted in the discontinuation of 6.5% (12/184) of the 0.15% group, 5.9% (11/186) of the 0.2% group, and 7.6% (14/184) of the ALPHAGAN group (p=0.804). Serious adverse events were reported for 2.7% (5/184) of patients receiving Brimonidine-Purite 0.15%, 2.7% (5/186) of patients receiving Brimonidine-Purite 0.2%, and 3.3% (6/184) of patients receiving ALPHAGAN (p=0.934).

One death was reported during the study in the 0.2% group secondary to a cerebrovascular accident: This was an 85 year old woman with a history of hypertension and cerebrovascular accidents, and had been diagnosed with atrial fibrillation.

Table 24 -Serious Adverse Events – Study 008

Patient Number	Treatment	Adverse Event	Outcome	Discontinued from Study
1655-J01	Brimonidine-Purite 0.15%	Peripheral Vascular Disorder	Recovered w/o Sequele	No
1655-J05	Brimonidine-Purite 0.15%	Bone Fracture	Recovered w/o Sequele	No
1960-Y04	Brimonidine-Purite 0.15%	Cholelithiasis	Recovered w/o Sequele	No
2972-U13	Brimonidine-Purite 0.15%	Carcinoma	Recovered w/o Sequele	No
2983-E02	Brimonidine-Purite 0.15%	Arrhythmia	Recovered w/o Sequele	No
0565-X09	Brimonidine-Purite 0.2%	Endometrial Carcinoma	Recovered w/o Sequele	No
1512-D18	Brimonidine-Purite 0.2%	Bradycardia	Recovered w/o Sequele	No
1584-A01	Brimonidine-Purite 0.2%	Angina Pectoris	Recovered w/o Sequele	No
1587-H16	Brimonidine-Purite 0.2%	Coronary Artery Disorder	Recovered w/o Sequele	No
2122-T21	Brimonidine-Purite 0.2%	Cerebrovascular Accident	Death	Yes
2980-W20	ALPHAGAN	Pancreatitis	Recovered w/o Sequele	No
2980-W23	ALPHAGAN	Cerebral Ischemia	Recovered w/o Sequele	No
2980-W31	ALPHAGAN	Manic Depressive Reaction	Recovered w/o Sequele	No
2981-N01	ALPHAGAN	Tachycardia	Recovered w/o Sequele	No
2983-E32	ALPHAGAN	Chest Pain	Recovered w/o Sequele	No
2984-C14	ALPHAGAN	Neuropathy	Recovered w/ Sequele	No

Visual Acuity

For visual acuity, all analyses were performed on the eye with the most unfavorable change from baseline as this was the most conservative evaluation. Changes in visual acuity as determined by changes in line number comparing the patient's final evaluation to baseline were analyzed. At the final visit, there were no significant differences among the treatment groups

Table 25 -Visual Acuity Change from Baseline-Study 008

[illegible]	[illegible]	[illegible]	[illegible]
≤-2	14 (7.7%)	13 (7.0%)	13 (7.1%)
> -2 to ≤ -1	35 (19.1%)	42 (22.7%)	44 (23.9%)
> -1 to < 0	20 (10.9%)	27 (14.6%)	28 (15.2%)
0	99 (54.1%)	76 (41.1%)	74 (40.2%)
> 0 to < 1	8 (4.4%)	10 (5.4%)	14 (7.6%)
≥ 1 to < 2	4 (2.2%)	17 (9.2%)	10 (5.4%)
≥ 2	3 (1.6%)	0 (0.0%)	1 (0.5%)

Reviewer's Comments: *There were no statistically significant among group differences in the worsening of visual acuity by ≥ 2 lines of visual acuity.*

Cup-Disc Ratio

For cup/disc ratio, the analysis was performed on the eye with the most unfavorable change from baseline. A similar pattern of distribution of worst change from baseline in cup/disc ratio at month 3 was seen among the treatment groups.

Table 26 - Cup-Disc Ratio Change from Baseline at Month 3 – Study 008

[illegible]	[illegible]	[illegible]	[illegible]
≤ -0.2	1 (0.5%)	1 (0.5%)	0
> -0.2 to ≤ -0.1	4 (2.2%)	7 (3.8%)	6 (3.3%)
> -0.1 to < 0	6 (3.3%)	4 (2.2%)	3 (1.6%)
0	148 (80.4%)	153 (82.7%)	147 (79.9%)
> 0 to < 0.1	10 (5.4%)	6 (3.2%)	11 (6.0%)
≥ 0.1 to <0. 2	8 (4.3%)	12 (6.5%)	14 (7.6%)
≥ 0.2	7 (3.8%)	2 (1.1%)	3 (1.6%)

Endothelial Cell Count

The endothelial cell count analyses was performed on the eye with the most unfavorable change from baseline. Endothelial cell count data were collected at 8 sites in a total of 244 patients. There was no statistically significant difference among treatment groups in endothelial cell count at baseline or the change from baseline at month 3 ($p \geq 0.169$)

Table 27 - Mean Endothelial Cell Count – Study 008

	Brimonidine-Purite 0.15%	Brimonidine-Purite 0.2%	Alphagan
Baseline	2215.3	2317.9	2268
Month 3	2156.4	2308.7	2251.9

Reviewer's Comments: *There were no clinically significant changes in endothelial cell count between baseline and 3 months in any of the treatment groups.*

Cardiovascular

There was no clinically significant changes between or within group differences with respect mean changes from baseline for heart rate and blood pressure at month 3.

Reviewer's Summary of Safety and Efficacy

Brimonidine-Purite 0.15% has an IOP lowering ability which is equivalent to Alphagan.

The average IOP lowering capability of Brimonidine-Purite 0.15% and 0.2% range from approximately

Brimonidine-Purite 0.15%, 0.2% and Alphagan have similar adverse event profiles.

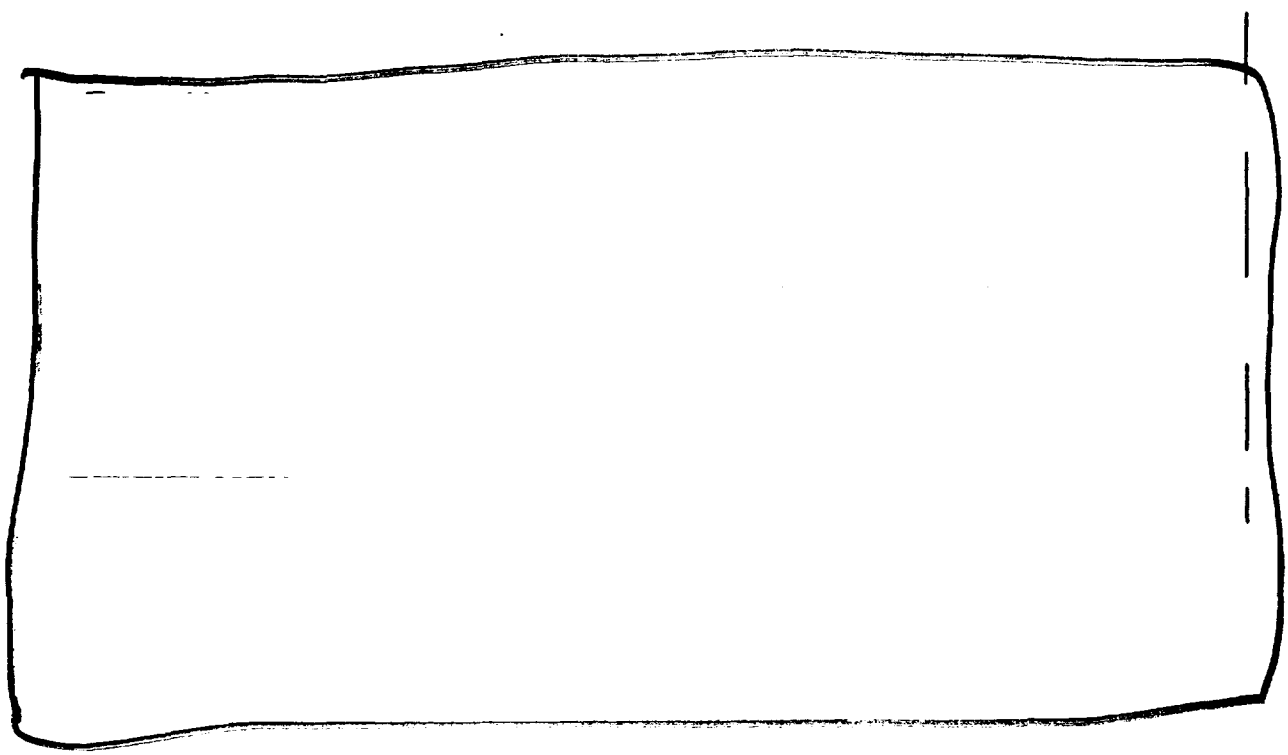
9 Reviewer's Overall Summary of Efficacy and Safety

Brimonidine-Purite 0.15% and 0.2% are equivalent to the currently marketed Alphagan in their ability to lower IOP in patients with ocular hypertension or open angle glaucoma.

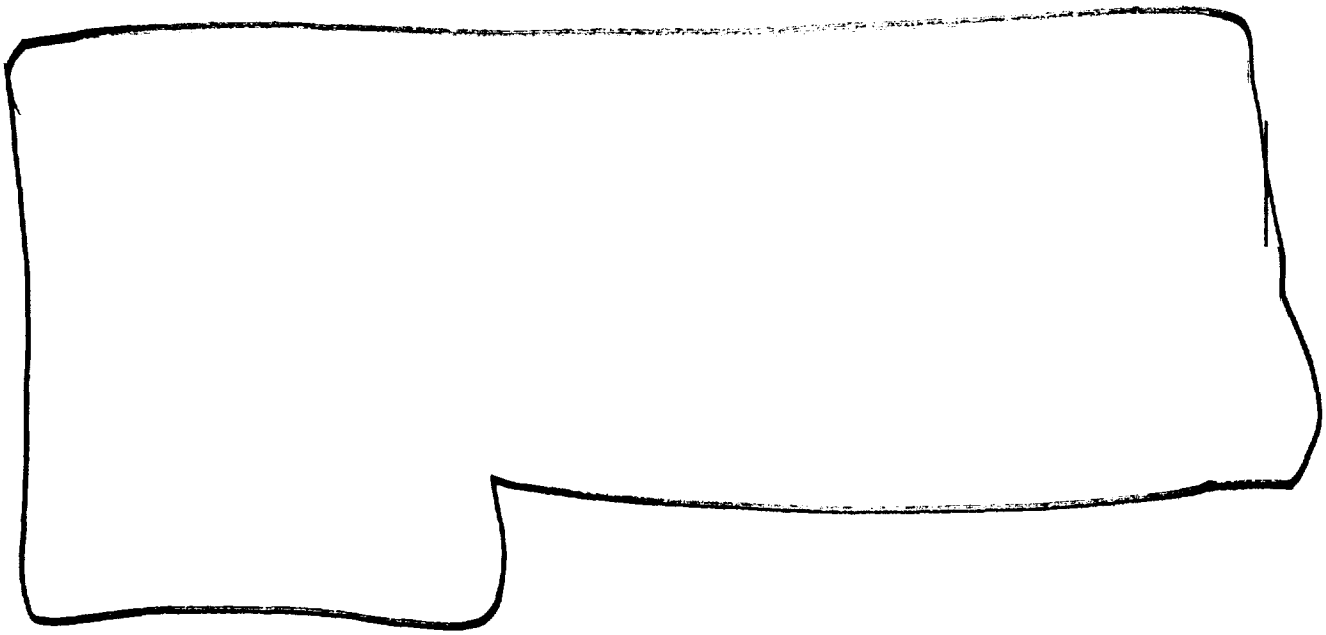
Adequate safety has been established for the use of Brimonidine-Purite 0.15% and 0.2% in lowering intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

10 Labeling Review

Reviewer's Comments:
Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.



5 page(s) of revised draft labeling has been redacted from this portion of the review.



APPEARS THIS WAY
ON ORIGINAL

11 Conclusions

The submitted studies demonstrate safety and efficacy for the use of Brimonidine-Purite 0.15% in lowering intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

12 Recommendation

1. *Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-262 is recommended for approval for lowering intraocular pressure in patients with ocular hypertension or open-angle glaucoma.*

2. *The applicant should submit revised labeling consistent with the recommendations in this review.*

/S/

Jennifer D. Harris, M.D.
Medical Officer, Ophthalmology

cc:
NDA 21-262
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers /S/ 11/2/00
HFD-550/Chem/Rodriquez
HFD-550/PM/Gorski
HFD-550/Pharm/Mukherjee
HFD-805/Micro/
HFD 550/Stat/Li
HFD 550/PK/Tandon
HFD-340/Carreras

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